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PRINCIPAL INVESTIGATOR: Leon Sun, M.D., Ph.D.
Judd W. Moul
Hongyu Wu
Fatiha Bensouda
Holly Wu
Mohammed Berrada

CONTRACTING ORGANIZATION: Henry M. Jackson Foundation for the Advancement of Military Medicine
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Leon Sun, M.D., Ph.D., Judd W. Moul, Hongyu Wu, Fatiha Bensouda, Holly Wu, Mohammed Berrada

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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Email: ssrivastava@cpdr.org

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13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

The objective of the development of Internet-accessible prediction models is to enhance the diagnosis accuracy, treatment efficacy and prognosis for patients with carcinoma of prostate cancer (CaP). An Oracle database was created, and Internet-accessible data collection applications were developed. Program packages for daily data retrieval, standardization, and reorganization were built. The roles of variables (race/ethnicity, diagnostic age, labs and treatment types) on the outcome of CaP patients were analyzed. The results show that CaP patients who chose watchful waiting tend to be older with lower serum PSA and lower Gleason score. The age at diagnosis, diagnostic PSA and clinical T-stage are the most significant predictors of secondary treatment in watchful waiting (submitted to J Urol). Pre-treatment testosterone level is a predictor of PSA recurrence (accepted for publication in J Urol). Post-treatment PSA doubling time < 3 months is a surrogate for prostate cancer specific mortality following surgery or radiation therapy (submitted to J Urol). Biostatistical models with variables of race, pre-treatment PSA, clinical stage, pathological stage and Gleason sum for predicting PSA recurrence before and after radical prostatectomy were implemented on CPDR webpage (www.cpdr.org). Further data analysis and the development of the prediction models are in progress.

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INTRODUCTION

The task of advising patients regarding prostate cancer (CaP) treatment options remains extremely challenging because of the great complexity of the interactions among many prognostic factors affecting the clinical course of the disease [1-4]. This study seeks to ameliorate this problem by developing software to examine a comprehensive retrospective database of prostate cancer patients and subjects of prostate cancer screening in order to generate statistical outcome likelihoods for different combinations of prognostic and diagnostic factors and treatment options. The products from this study are aimed to improve early and accurate diagnosis and proper treatment of CaP, thereby lowering healthcare costs and raising survival rates. The function of predicting post-therapy recurrence and optimal recurrence treatment would assist physicians to implement rational clinical interventions, thereby optimizing patients' quality of life and prolonging life expectancy as well.

For the above purposes, we proposed to: (1) Analyze the data by integrating the most powerful prognostic variables in three regression models: logistic regression, Cox proportional regression, and artificial neural networks; (2) Build clinical models predicting probability of prostate cancer in the diagnosis phase, optimal primary treatment in the treatment phase, and optimal recurrence treatment and outcome in the follow-up phase; (3) Post these models as software on the Internet, accessible by patients and physicians as tools for public education, patient self-test, and physician's decision support reference.

Clinical model development includes five phases: (1) Data preparation: Clinical data will be retrieved from the CPDR National Database, sorted, standardized, and mapped into categories of diagnosis, treatment, follow-up; (2) Data warehousing: The data will be stored into a data warehouse; (3) Data analysis: Traditional statistical methods and/or other new mathematical and computational tools such as decision tree system and artificial neural networks will be used to analyze the effect of each parameter and the interactions of the factors on the CaP clinical process; (4) Data modeling: The probability and confidence range for CaP early detection, optimal primary treatment, treatment of recurrence, and treatment of late-stage disease will be calculated for each of the combinations of the input variables to establish prediction models; (5) Web application development: The developed models will be programmed and posted on the CPDR webpage.

BODY

The development schedule and progress of this project are based on the Statement of Work of the research proposal.

In the first year of the grant proposal we have focused on data collection, defining prognostic variables, preparation of program packages for data retrieval and standardization, design and development of a data warehouse for storing the data sets dynamically used by the prediction models, analysis of data sets and creating prediction models.

1. Daily data collection.

As of the end of December 2002, the DoD-CPDR National Database contains 433,083 records on 17,469 men (Table 1). It is one of the largest and most comprehensive longitudinal prostate cancer databases in the nation and world. The data from consented patients was daily collected by well-trained CPDR staff with the standardized database implemented in nine military hospitals across the country (Table 2). At each CPDR site, there is one military physician as principal investigator, and 1-2 military physicians as associate investigators.

Several issues are critical to the prostate cancer database used for a decision supporting system: (1) Data must be from many institutions located in different geographic areas to provide unbiased statistical results; (2) Data must be from multiple disciplines (urology, radiation oncology and medical oncology) to include and integrate the data of multiple treatments for a single patient; (3) Data quantity must be large enough to meet most clinical situations of individual patients; and (4) The data collection must be longitudinal to keep the decision support system updated and validated. The CPDR National Database meets all these requirements. These unique features of the CPDR National Database provide a solid foundation for the success of the proposed study. The results and products derived from this database have every likelihood of being reliable, representative, practical, and beneficial.

Table 1. Records stored in the CPDR National Database (as of the end of December 2002)

Site	BAMC	EAMC	MAMC	MGMC	NMCP	NMCSD	NNMC	WHMC	WRAMC	Total
Biopsy	2321	815	2058	1504	1492	2527	2137	1826	5452	20132
Brachytherapy	45	20	57	19	61	33	101	181	113	630
Cryotherapy	3	3				4	1		19	30
Follow-Up1	8171	1566	11923	6205	12290	21445	21419	12448	20228	115695
Follow-Up2	5758	1550	8314	2584	12098	21045	5811	5590	19944	82694
General_Info	1803	685	1698	1366	1128	1974	2048	1282	4889	16873
Hormonal	744	886	916	1148	1519	1967	1112	2941	2146	13379
Lab Results*									66873	66873
Med History	1620	685	1524	1080	1115	1970	1639	1268	4008	14909
Necropy	136	94	456	177	276	271	377	130	1477	3394
Pathology	489	226	531	432	378	904	597	686	1525	5768
Contact info	1688	685	1610	1280	1119	1973	1987	1280	4926	16548
Prostatectomy	499	231	552	465	377	980	636	694	1690	6124
Radiation Dose	228	180	474	80	351	559	534	163	1449	4018
Radiation Tx	246	201	501	189	484	605	891	191	1649	4957
Registration	1802	685	1769	1418	1128	1974	2168	1285	5240	**17469**
Staging	984	665	1367	827	1050	1702	1579	1233	3924	13331
Survey	98	94	159	108	9	396	499	54	2833	4250
TRUS	2345	819	2102	1513	1504	2517	2054	1828	6449	21131
Tumor Size	14	11	22	756	6	462	15	332	3260	4878
Sum	**28994**	**10101**	**36033**	**21151**	**36385**	**63308**	**45605**	**33412**	**158094**	**433083**

Table 2. Hospitals and their locations with an active CPDR database

Abbreviation	Full Name	City	State
BAMC	Brook Army Medical Center	Ft. Sam Houston	Texas
EAMC	Eisenhower Army Medical Center	Ft. Gordon	Georgia
MAMC	Madigan Army Medical Center	Tacoma	Washington
MGMC	Malcolm Grow Medical Center	Andrews AFB	Maryland
NMCP	Naval Medical Center	Portsmouth	Virginia
NMCSD	Naval Medical Center	San Diego	California
NNMC	National Naval Medical Center	Bethesda	Maryland
WHMC	Wilford Hall Medical Center	Lackland AFB	Texas
WRAMC	Walter Reed Medical Center	Washington	District of Columbia

2. Watchful waiting

Watchful waiting remains an important treatment option for CaP patients [5-10]. We attempted to verify the demographic, clinical and outcome features of watchful waiting. We also attempted to gain an understanding of what leads men to choose "watchful waiting" and discover the predictive factors of secondary treatment.

1. Prognostic factors for watchful waiting and its outcome (Appendix 1, accepted as podium presention in AUA 2003 and submitted to J Urol). Of the 8,390 patients diagnosed with prostate cancer from 1990 to 2001 in the DoD-CPDR National Database, 1,158 underwent watchful waiting as their initial treatment. The differences in demographic and clinical data between watchful waiting patients and other patients were compared using the chi-square test. The Kaplan-Meier and log-rank test were used to test the differences of secondary treatment-free survival between prognostic factors. The multivariate Cox proportional hazard regression analysis was performed to determine the independent significant predictors of the secondary treatment.

Results show that patients selecting watchful waiting were older at diagnosis, had lower diagnostic PSA, had a higher percentage of T1 stage and a higher percentage of Gleason score of 7 or less. Age at diagnosis, diagnostic PSA and clinical stage were independent significant predictors of secondary treatment. The relative risk (RR) of secondary treatment can be expressed as RR= EXP (-0.034* age at diagnosis + 0.284* LOG (diagnostic PSA) + 0.271* clinical stage T2 + 0.264* clinical stage T3). The patients receiving secondary treatment were divided into three risk groups based on RR of secondary treatment as low (0 - 0.13), intermediate (0.14 -0.19), and high (> 0.19). The secondary treatment-free survival analysis stratified by risk group revealed a significant difference in the risks of secondary treatment among these three risk groups ($p < 0.0001$, Figure 1).

2. Outcome of watchful waiting in low risk localized prostate cancer in men under age 70 in the PSA era (Apendix 2, to be submitted to J Urol 2003). 313 men were identified who had median length of follow-up of 3.8 years. Median age at diagnosis was 65.4 years (range 41-70). Ninety- eight (31%) men have remained on watchful waiting, while 215 (69%) have proceeded to secondary therapy. Of those who underwent

secondary treatment, 57.3% and 73.2% elected to do so within the first 2 and 4 years after diagnosis, respectively. The median PSA doubling time was 2.5 years for those who progressed to therapy; those who remained on watchful waiting had a median doubling time > 10 years. For patients electing secondary treatment, the type of therapy treatment they underwent was associated with the number of patient co-morbidities ($p = 0.012$). Patients with fewer co-morbidities were more likely to choose radical prostatectomy or brachytherapy. Cox model shows that clinical stage and PSA doubling time are the prognostic factors (Table 3).

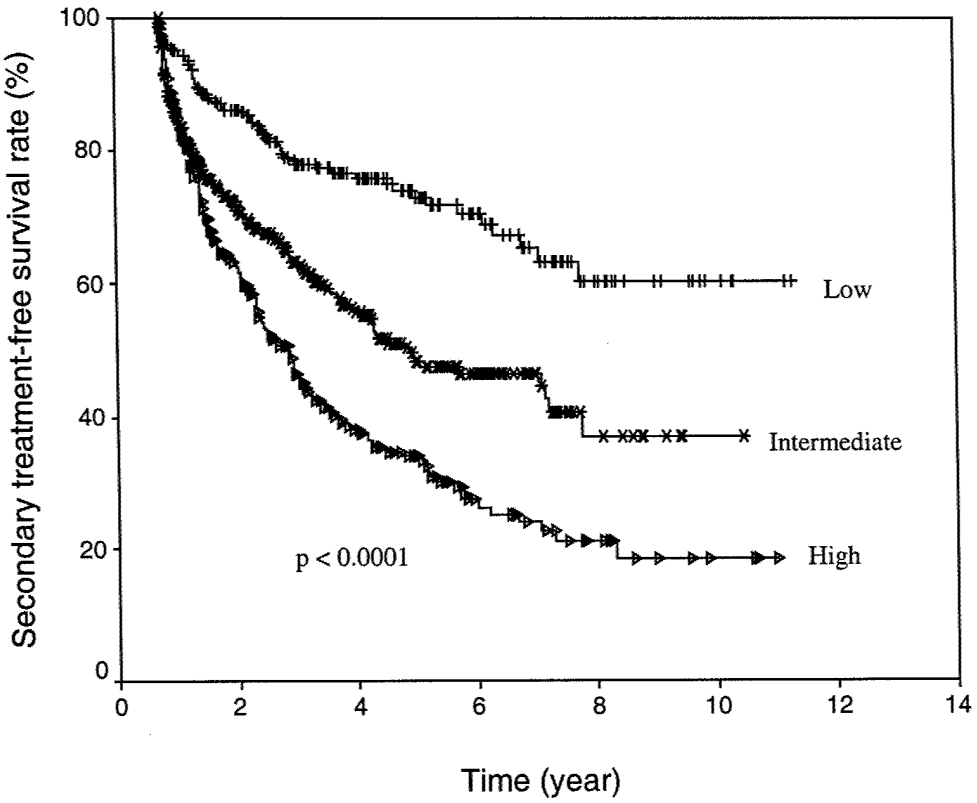

Figure 1. Secondary treatment-free survival group in watchful waiting patients stratified by risk group

Table 3. Cox proportional hazards model for predictors of secondary treatment

Risk of secondary treatment	Hazards Ratio	95% CI	p Value
Clinical Stage			
cT1c vs. cT1a/b	7.077	1.642-30.498	0.0087
cT2a vs. cT1a/b	5.647	1.260-25.302	0.0237
cT2b vs. cT1a/b	9.184	1.933-43.644	0.0053
cT2c vs. cT1a/b	16.400	3.159-85.157	0.0009
PSA Doubling time			
2-5 vs. <2	0.325	0.202-0.523	<0.0001
5.1-50 vs. <2	0.116	0.063-0.212	<0.0001
>50 vs. <2	0.133	0.073-0.242	<0.0001
Age			
60-65 vs. <60	1.067	0.646-1.762	0.7997
65-70 vs. <60	0.736	0.428-1.268	0.2700
PSA at diagnoses			
4.1-10.0 vs. 0-4.0	1.311	0.751-2.287	0.3410
10.1-20.0 vs. 0-4.0	1.069	0.523-2.184	0.8559
Gleason score			
5 vs. 2-4	1.017	0.613-1.689	0.9477
6 vs. 2-4	1.450	0.914-2.301	0.1148
Number of comorbidities per patient			
1 vs. 0	1.022	0.649-1.610	0.9259
2 vs. 0	0.861	0.516-1.436	0.5658
Family History of CaP			
Yes vs. No	1.376	0.868-2.183	0.1748
Race			
Caucasian vs. African American	1.131	0.726-1.763	0.5861

3. PSA doubling post radical prostatectomy is surrogate disease-specific death (Appendix 3, accepted as moderated poster in AUA 2003 and submitted to Journal of the National Cancer Institute 2003)

While essentially always found in conjunction with an asymptomatic patient, prostate-specific antigen (PSA) failure following initial therapy with either radical prostatectomy (RP) or external beam radiation therapy (RT) is considered treatment failure. Therefore, PSA failure is often used as the trigger to initiate secondary therapy [10-11] However, whether PSA failure given time will translate into prostate cancer specific mortality (PCSM), particularly for men with competing causes of mortality, remains unknown [12-13].

8,669 men treated with either surgery (N = 5918) or radiation (N = 2751) from 1988 to 2002 for clinical stage T1c-4NxMo prostate cancer were used for the study cohort. The PSA DT interval selected for study as a possible surrogate of PCSM corresponded to the maximum time interval that minimized the difference in the estimates of PCSM and all cause mortality (ACM) following PSA failure. Prentice's criteria require that the surrogate was a prognostic factor and that the treatment utilized did not alter the time to PCSM following achievement of the surrogate. These criteria were tested using Cox regression.

The maximum value of the PSA DT interval that minimized the difference in the estimates of PCSM and ACM following PSA failure was < 3 months. A PSA DT < 3 months was a significant predictor of both time to PCSM ($p_{Cox} < 0.0001$) and time to ACM ($p_{Cox} < 0.0001$) following PSA failure. The treatment received was not a significant predictor of time to

PCSM (p_{Cox} = 0.37) or ACM (p_{Cox} = 0.67) following PSA failure for patients with a PSA DT < 3 months.

4. Pretreatment testosterone level is a prognostic factor to predict extraprostatic disease in localized prostate cancer patients (Appendix 4, accepted as moderated poster by AUA 2003 and by J Urol for publication).

Low levels of pretreatment serum total testosterone consistently predict more aggressive disease, worse prognosis, and worse treatment response in patients with metastatic prostate cancer [14-17]. Prior studies have not demonstrated this same correlation in patients with known localized disease. We sought to rigorously test pretreatment total testosterone levels as a potential staging and prognostic marker in a large cohort of 879 radical prostatectomy patients with localized cancer. The patients were operated upon between January 1, 1986 and June 30, 2002 at nine hospital sites. Nonparametric tests were used to compare the relationship of pretreatment testosterone to other variables. Multivariate logistic regression analysis was used to assess for clinical predictors of extraprostatic disease. Kaplan Meier survival methods and Cox regression analysis were used to assess predictors of biochemical recurrence. The results show that patients with non-organ-confined prostate cancer (pT3-T4) showed significantly lower pretreatment total testosterone levels than those with organ-confined cancer (pT1-T2) (Nonparmetric p = 0.041). In multivariate analysis, pretreatment total testosterone emerged as a significant independent predictor of extraprostatic disease (p = 0.046, Figure 2). Total testosterone was not a significant predictor of biochemical (PSA) recurrence (p = 0.467).

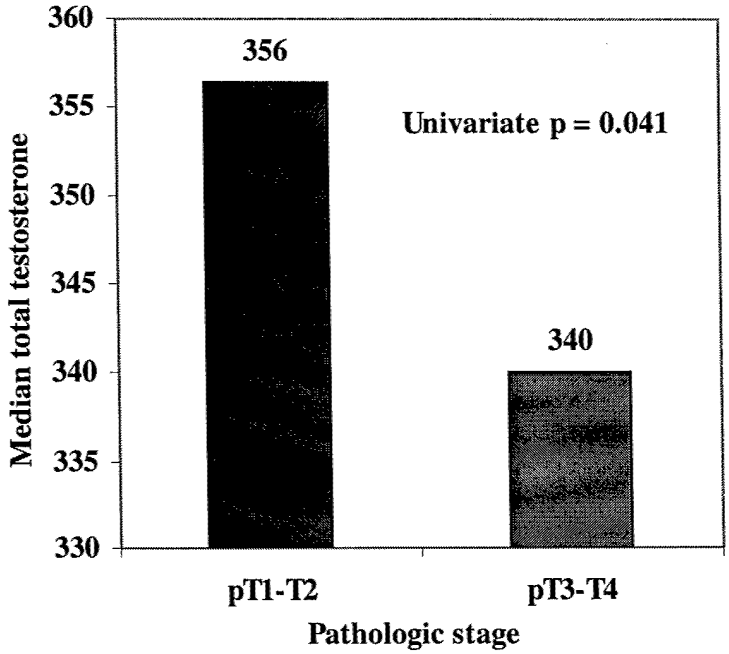

Figure 2. Low pretreatment total testosterone levels predict extraprostatic disease in radical prostatectomy patients

5. Implementation of predicting models in CPDR webpage accessible through the Internet (http://www.cpdr.org/PreOpInput.html **and** http://www.cpdr.org/PostOpInput.html)**.**

Biostatistical models predicting the risk of recurrence after radical prostatectomy for clinically localized prostate cancer are created based on 4205 radical prostatectomy patient data. In our analysis we evaluated age, race, prostatic acid phosphatase and nuclear grade with the established prognostic variables of pretreatment prostate specific antigen, postoperative Gleason sum and pathological stage.

After multivariate Cox regression analysis using only statistically significant variables that predicted recurrence, we developed an equation that calculates the relative risk of recurrence (RR) after surgery. This model was validated with an independent cohort of radical prostatectomy patients treated at different medical centers by multiple primary surgeons. Figure 3 shows the webpage with the model predicting PSA recurrence with pretreatment variables and Figure 4 shows the model predicting PSA recurrence with pathological variables in patients post radical prostatectomy.

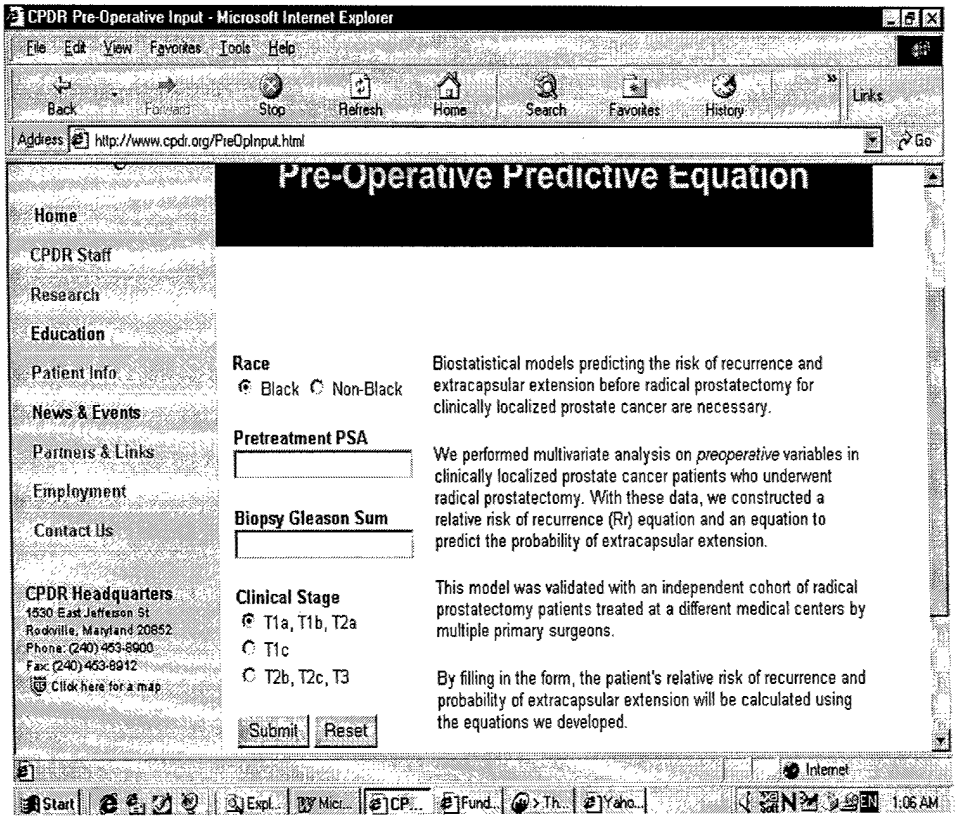

Figure 3. Predicting relative risk of PSA recurrence with pretreatment variables

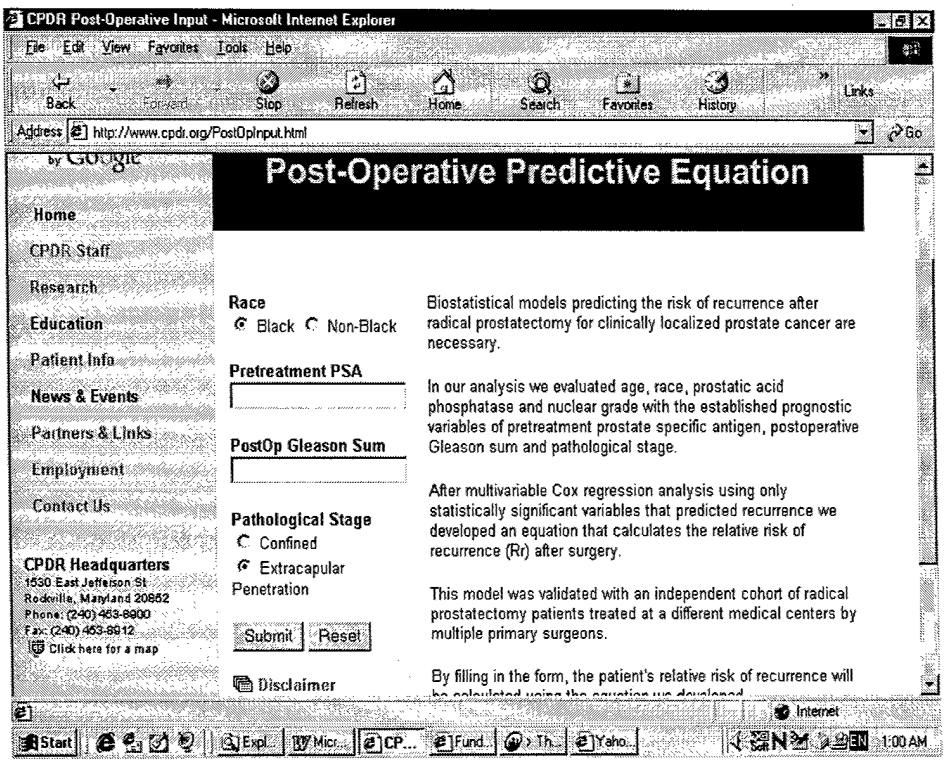

Figure 4. Predicting relative risk of PSA recurrence post radical prostatectomy

KEY RESEARCH ACCOMPLISHEMTS

- Created an Oracle database
- Created a data warehouse
- Analyzed the roles of pretreatment (testosterone, PSA, Gleason, Clinical stage, Age, Race, and posttreatment (PSA doubling time) variables on the outcome of prostate cancer
- Identified the epidemiology of watchful waiting and the factors associated with secondary treatment
- Analyzed the natural history of radical prostatectomy (Appendix 5, accepted as moderated poster in AUA 2003)
- Established an algorithm with preoperative variables to predict PSA recurrence in prostate cancer patients receiving radical prostatectomy (Appendix 6, accepted as moderated poster in AUA 2003)
- One article was accepted for publication
- Two articles were submitted for publication
- One manuscript is ready to be submitted for publication
- There abstracts were accepted as moderated posters by AUA 2003
- One abstract was accepted as podium presentation by AUA 2003
- Two web applications were implemented on the CPDR webpage to predict relative risk of PSA recurrence with pretreatment variables and pathological variables.

REPORTABLE OUTCOMES

- Men who chose watchful waiting for prostate cancer tend to be older with lower serum PSA and lower Gleason score. The age at diagnosis, diagnostic PSA and clinical T-stage are the most significant predictors of secondary treatment in watchful waiting.

- Even carefully selected patients under age 70 who initially elect watchful waiting in the PSA era have a 57.3% chance of progressing to definitive treatment in the first 2 years after diagnosis and a 73.2% chance within 4 years. Patients with faster PSA doubling times and higher clinical stage disease (T2b or T2c) were statistically more likely to abandon the strategy of watchful waiting in favor of seeking definitive therapy. While the number and type of major co-morbidities did not predict whether patients would progress to secondary therapy, it did influence the type of definitive therapy ultimately chosen. This treatment strategy may be better termed Temporary Deferred Therapy (TDT) in the PSA era.

- A posttreatment PSA DT < 3 months is a surrogate for prostate cancer specific mortality.

- Pretreatment total testosterone was an independent predictor of extraprostatic disease in localized prostate cancer patients. As testosterone decreases, patients have a higher likelihood of non-organ-confined disease. Low testosterone was not predictive of biochemical recurrence.

CONCLUSIONS

More than 50% of patients who choose watchful waiting as their initial treatment option will receive secondary definitive treatment. Pretreatment total testosterone level is a surrogate for extracapsular extension of CaP. Posttreatment PSA doubling time < 3 months is significantly associated with disease-specific death. Taken together, these data indicate that using pretreatment and posttreatment variables to predict CaP outcome is practical; this practice will lead us to better understand prostate cancer's clinical course and improve clinical management. A comprehensive effort is underway to develop more prediction models and to post these models on the web, accessible by physicians and patients for their decision making.

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APPENDICES

1. Hongyan Wu, Leon Sun1, Judd W. Moul, Julian Wu, David G. McLeod, Christopher Amling, Raymond Lance, Leo Kusuda, Timothy Donahue, John Foley, Andrew Chung, Wade Sexton, Douglas Soderdahl. Watchful waiting and predicting factors for secondary treatment in prostate cancer. J Urol 2003 (Pending, accepted as podium presentation in AUA 2003)

2. Corey A. Carter, Timothy Donahue, Leon Sun, Hongyu Wu, David G. McLeod, Christopher Amling, Raymond Lance, John Foley, Wade Sexton, Leo Kusuda, Andrew Chung, Douglas Soderdahl, Stephen Jackman, Judd W. Moul. Temporary-deferred therapy (TDT) (watchful waiting) in low risk localized prostate cancer in men under age 70 in the psa era: results of

the department of defense (DoD) center for prostate disease research (CPDR) national database. To be submitted to J Urol 2003

3. Anthony V. D'Amico, Judd Moul, Peter R. Carroll, Leon Sun, Deborah Lubeck, Ming-Hui Chen. Surrogate marker for prostate cancer specific mortality following radical prostatectomy or radiation therapy. J National Cancer Inst 2003 (Pending, Accepted as moderated poster by AUA 2003)

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5. Julian Wu, Leon Sun, Judd W. Moul, Holly Wu, David G. McLeod, Christopher Amling, Raymond Lance, John Foley, Wade Sexton, Leo Kusuda, Andrew Chung, Douglas Soderdahl, Timothy Donahue, Lionel Banez.An algorithm with preoperative variables to predict PSA recurrence in prostate cancer patients receiving radical prostatectomy (Accepted as moderated poster in AUA 2003)

6. Leon Sun, Judd W. Moul, Julian Wu, David G. McLeod, Christopher Amling, Raymond Lance, John Foley, Wade Sexton, Leo Kusuda, Andrew Chung, Douglas Soderdahl, Timothy Donahue, Michelle Zhao, Jack Chang. (Accepted as moderated poster in AUA 2003)

Apendix 1 (Accepted as podium presentation by AUA 2003 and submitted to J Urol for publication)

WATCHFUL WAITING AND PREDICTING FACTORS FOR SECONDARY TREATMENT IN PROSTATE CANCER

Hongyan Wu[1], Leon Sun1[1], Judd W. Moul[1,2], Julian Wu[1], David G. McLeod[1,2], Christopher Amling[1,3], Raymond Lance[1,4], Leo Kusuda[1,5], Timothy Donahue[1,6], John Foley[1,7], Andrew Chung[1,8], Wade Sexton[1,9], Douglas Soderdahl[1,10]

1. Center for Prostate Disease Research (CPDR), Department of Surgery
   Uniformed Services University of the Health Sciences, Bethesda, MD 20814
2. Urology Service, Department of Surgery, Walter Reed Army Medical Center, Washington, D.C. 20307
3. Department of Urology, San Diego Naval Medical Center, San Diego, CA
4. Urology Service, Dept. of Surgery, Madigan Army Medical Center, Tacoma, WA
5. Department of Urology, Portsmouth Naval Medical Center, Portsmouth, VA
6. Department of Urology, National Naval Medical Center, Bethesda, MD
7. Urology Service, Dept. of Surgery, Brooke Army Medical Center, San Antonio, TX
8. Department of Urology, Malcolm Grow Medical Center, Andrews AFB, MD
9. Department of Urology, Wilford Hall Medical Center, Lackland AFB, TX
10. Urology Service, Dept. of Surgery, Eisenhower Army Medical Center, Augusta, GA

Requests for reprints/correspondence:
Leon Sun, MD, PhD and Judd Moul, MD
Center for Prostate Disease Research
1530 East Jefferson Street, Rockville, MD 20852
Telephone: (240) 453-8922
Fax: (240) 453-8912
Email: lsun@cpdr.org, jmoul@cpdr.org

Key Words:
Prostate cancer, Watchful waiting, Prognostic factor, Secondary treatment, Prostate-specific antigen

Running Title: Watchful waiting and factors for treatment

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ABSTRACT

PURPOSE: Watchful waiting remains an important treatment option for patients. We attempted to verify the demographic, clinical and outcome features of watchful waiting. We also attempted to gain an understanding of what leads men to choose "watchful waiting" and discover the predicting factors of secondary treatment.

MATERIALS AND METHODS: Out of 8390 patients diagnosed with prostate cancer from 1990 to 2001 in the DoD CPDR Database, 1158 patients underwent watchful waiting as their initial treatment. The differences in demographic and clinical data between watchful waiting patients and other patients were compared using the chi-square test. The Kaplan-Meier and log-rank test were used to test the differences of secondary treatment-free survival between prognostic factors. The multivariate Cox proportional hazard regression analysis was performed to determine the independent significant predictors of the secondary treatment.

RESULTS: Patients selecting watchful waiting were older at diagnosis, had lower diagnostic PSA, had a higher percentage of T1 stage and a higher percentage of Gleason score of 7 or less. Age at diagnosis, diagnostic PSA and clinical stage were independent significant predictors of secondary treatment. The relative risk (RR) of secondary treatment can be expressed as RR= EXP (-0.034* age at diagnosis + 0.284* LOG (diagnostic PSA) + 0.271* clinical stage T2 + 0.264* clinical stage T3).

CONCLUSIONS: Men who chose watchful waiting for prostate cancer tend to be older with lower serum PSA and lower Gleason score. The age at diagnosis, diagnostic PSA and clinical T-stage are the most significant predictors of secondary treatment in watchful waiting.

INTRODUCTION

Prostate cancer is the most common tumor identified in American men and the secondary leading cause of cancer-related death.[1] Since the introduction of the prostate-specific antigen (PSA) screening test in the late 1980s and an increase in public awareness of the disease that occurred in the early 1990s, the number of prostate cancer cases diagnosed over the past decade has increased dramatically, leading to both a stage migration toward more localized disease and a trend toward younger age at the time of diagnosis.[2]

Major initial local treatment alternatives for prostate cancer include radical prostatectomy, external beam radiotherapy, radioactive seed implant brachytherapy, cryotherapy and watchful waiting.[3] The optimal management of prostate cancer remains controversial. The primary benefits hypothesized for definitive treatment (radical prostatectomy, radiation therapy and cryotherapy) are reduction in the risk of subsequent development of metastatic disease and ultimately death from the disease. Given the natural history of conservatively managed prostate cancer and the advanced age of many men at diagnosis, watchful waiting remains an important treatment option for patients with less than 10 years life expectancy and for patients with multiple comorbidities that may preclude active treatment. Retrospective studies indicated that watchful waiting may be suitable for intermediate or low-risk disease and should be assigned based on clinical T stage, serum PSA at diagnosis and biopsy Gleason score. However, it is still uncertain what the optimal treatment is for intermediate or low-risk disease, whether some patients with early cancer can be managed expectantly, and how these patients might be recognized. The DoD-CPDR Database contains a large cohort of watchful waiting patients enrolled between 1990 and 2001, allowing an analysis of demographic, clinical and outcome features of watchful waiting. Additionally, we attempted to determine factors significantly associated with receiving secondary treatment and to build a model to predict the likelihood of secondary treatment of watchful waiting.

MATERIALS AND METHODS

The clinical information and follow-up have been collected as part of the DoD-CPDR Tri-Service Multicenter Prostate Disease Research Database as described previously by Sun et al.[4] Briefly,

standardized data collection forms for registration, prostatic biopsy, staging, treatment (watchful waiting, surgery, radiation treatment, hormonal treatment and cryotherapy), follow-up, and necropsy were used. Data was collected and entered by physicians and CPDR full-time, in-hospital data managers, then maintained in a relational database using Oracle software. This project is under an approved protocol by the Institutional Review Board of Uniformed Services University as well as all participating military hospitals.

The data query for this study was performed in July 2002. At this time, the overall database contained 345,954 clinical records (i.e., TRUS/biopsy, staging, watchful waiting, follow-up, etc.) on 15,063 men. A total of 8739 prostate cancer patients diagnosed in the PSA-Era between Jan 1, 1990 and Dec 31, 2001 (12 years) was selected. Of these, 1158 patients received watchful waiting as their initial treatment, and 7232 received other primary treatments. There were 349 patients excluded from the study due to confirmed clinical metastasis (M1 disease) at diagnosis. Watchful waiting was defined as no active treatment after diagnosis for at least 9 months. Table I summarizes the number of patients and the type of primary treatment option. The mean and median follow-up time of the watchful waiting cohort were 3.5 years and 2.8 years (range from 0.8 to 11.3 years), respectively.

The data fields analyzed for this study included the patient's age at diagnosis, ethnicity/race, clinical stage at diagnosis, diagnostic prostate-specific antigen (PSA) value, highest (worst) biopsy Gleason sum, and family history of prostate cancer in a first or secondary degree relative. The number of comorbidities were divided into three separate groups: patients having no comorbidity, patients that have 1 comorbidity, and patients having more than 1 comorbidity at the time of diagnosis. Comorbidities collected by CPDR included chronic obstructive pulmonary disease, coronary artery disease, cerebral vascular accident, hypertension, renal insufficiency, diabetes, elevated cholesterol, and other cancers.

Demographics and clinical characteristics were compared in patients who remained on the watchful waiting protocol to those who underwent secondary treatment by using the chi-square test. Secondary treatment-free survival analysis was performed with the Kaplan-Meier (KM) log rank method.

The KM curves were further stratified by the patient's age, race, diagnosis PSA, Gleason score, clinical stage, combidities, and family history. A multivariate Cox proportional hazards regression model was constructed to assess the prognostic variables for secondary treatment in the watchful waiting cohort.

RESULTS

Mean and median age of patients receiving watchful waiting and active local treatment was 69.8 and 70.9, and 65.6 and 65.6 years old, respectively. Mean and median diagnosis PSA in watchful waiting patients was 15.1 and 6.4 ng/ml versus 15.3 and 7.1 ng/ml in the active local therapy patients. The comparison results of demographic and clinical factors between watchful waiting and active local therapy and between watchful waiting with and without secondary treatment are summarized in Tables 2 and 3, respectively. Compared with the active local therapy group, patients selecting watchful waiting were older at diagnosis (median: 70.9 versus 65.6, $p < 0.0001$), had lower diagnostic PSA (median: 6.4 versus 7.1, $p < 0.0001$), had higher percentage of T1 stage (53.6 % versus 41.3 %, $p < 0.0001$) and higher percentage of Gleason score of 7 or less (90.5% versus 84.0%, $p < 0.0001$). Out of 1158 watchful waiting patients, 453 patients (39.1%) progressed to secondary treatment (the median of follow-up time of the watchful waiting cohort is 2.8 years). Table IV shows the type of secondary treatment for patients who chose watchful waiting. Table V shows univariate analysis of factors associated with patients undergoing secondary treatment. The patient's age ($p = 0.0004$), race ($p < 0.0001$), clinical stage ($p < 0.0001$), diagnosis PSA ($p < 0.0001$) and highest biopsy Gleason sum ($p < 0.0001$) were significant factors associated with secondary treatment. Table VI shows a Kaplan-Meier analysis on the patient's ability to remain secondary treatment free. The 2- and 5-year secondary treatment free survival rates were stratified by age at diagnosis, race, clinical stage, diagnostic PSA, highest biopsy Gleason sum, family history, and number of comorbidities. The results indicate that race, clinical stage, and diagnostic PSA affect the risk of secondary treatment (log rank < 0.0001). Multivariate Cox regression analysis including age at diagnosis, race, diagnostic PSA, highest biopsy Gleason

sum, clinical stage, family history, and number of comorbidities found that age at diagnosis, diagnostic PSA and clinical stage were found to be significantly associated with secondary treatment (Table VII). Using only statistically significant variables to predict secondary treatment defined in the above multivariate analysis, an equation to calculate the relative risk (RR) of secondary treatment could be expressed as RR= EXP (-0.034* age at diagnosis + 0.284* LOG (diagnostic PSA) + 0.271* clinical stage T2 + 0.264* clinical stage T3). The patients receiving secondary treatment were divided into three risk groups based on RR of secondary treatment as low (0 - 0.13), intermediate (0.14 -0.19), and high (> 0.19). The 2-, 5- and 7-year secondary treatment-free survival of these patients is summarized in Table VIII. Figure I illustrates the Kaplan-Meier survival curve indicating the increased likelihood of secondary treatment over time. The secondary treatment-free survival analysis stratified by risk group revealed a significant difference in the risks of secondary treatment among these three risk groups ($p < 0.0001$, Figure II).

DISCUSSION

The most important finding at this multicenter contemporary PSA-Era experience with a large cohort of watchful waiting patients is that a large percentage of men progress to active local or systemic therapy in a relatively short period of time. Furthermore, clinical T-stage, age at diagnosis, and diagnostic PSA level were independent predictors at secondary therapy and our group was able to develop a clinically useful predictive equation for secondary therapy on watchful waiting. This equation, which is readily available on the Internet (www.cpdr.org), will give patients and clinicians the ability to estimate the success of a watchful waiting approach given the patient's age, stage, and PSA level.

The choice of treatment and management of prostate cancer is controversial, and no consensus guidelines are available on the proper treatment of the disease, especially for watchful waiting.[5] Different from nearly all other common human cancers, prostate cancer has the features of a high incidence of occult disease, an expanding elderly population with increased life expectancy and a slow natural history of

clinically-localized prostate cancer. Autopsy studies have shown a high incidence of clinically occult disease in aging men. Approximately 29%, 30%, 40%, and 67% of men in their fifth, sixth, seventh, and eighth decades of life, respectively, will have occult prostate cancer.[6] Autopsy studies have revealed that more than 10 million men in the U.S. have cancer in their prostate. The majority of prostate cancer patients is clinically insignificant.[7] Although the annual death rate from prostate cancer is high, several studies have noted that tumor progression may not occur or occur slowly in selected patients with clinically-localized cancers left untreated. The probability of tumor progression ranges between 30% and 72% depending on the length of follow-up.

Watchful waiting has been proposed as a reasonable treatment strategy for localized prostate cancer. Over the past decade many studies of watchful waiting analyzed the overall survival rate of patients electing such treatment. In these prospective and retrospective studies, there is indication that patients with localized prostate cancer electing watchful waiting may have no loss in life expectancy, and that it may be reasonable to initially avoid active local treatment.[8-10]

In 1997, Johansson et al. reported the disease-specific outcome of 642 patients diagnosed with prostate cancer in Sweden between the years 1977-1984.[8] Of the 300 men with localized prostate cancer, 233 received no initial therapy, followed by delayed treatment for symptomatic progression. In this group, 11% of the men with localized disease died of prostate cancer and the corrected 15-year survival rate was similar in 233 patients with deferred treatment (81%; 95% CI: 72%-89%) to those who were treated at the time of initial diagnosis (81%; 95% CI: 67%-95%). Men with poorly-differentiated disease had the highest death rate of prostate cancer (56%) compared to those with well- (7%) or moderately- (16%) differentiated disease.

In 1994, Chodak et al. reported a meta-analysis using 828 patients treated conservatively (with observation and delayed hormonal therapy but no radical surgery or irradiation) for clinically-localized prostate cancer from six non-randomized studies.[9] The 10-year disease-specific actuarial survival rates were 87%, 87% and 34% for tumor differentiation Grades I to III disease, while 10-year metastasis-free

survival rates were 81%, 58%, and 26% for Grades I to III disease, respectively. This study showed that the strategy of initial conservative management and delayed hormonal therapy is a reasonable choice for some men with Grade I or II clinically-localized prostate cancer, particularly for those who have an average life expectancy of 10 years or less. Their data supported the assertion that watchful waiting results in similar survival rates as compared to definitive treatment. Definitive treatment was seen as necessary for men with Grade III prostate cancer.

In 1995, Albertsen et al. reported results from 451 men diagnosed with clinically-localized prostate cancer in Connecticut between 1971 and 1976, and with mean follow-up of 15.1 years.[10] The age–adjusted survival for men with Gleason sum 2 to 4 tumors was not significantly different from that of the general population. Maximally-estimated lost life expectancy for men with Gleason sum 5 to 7 tumors was 4 to 5 years and for men with Gleason sum 8 to 10 tumors was 6 to 8 years. Tumor Gleason Grade and patient comorbidities were powerful independent predictors of survival.

Although watchful waiting may prevent the opportunity to cure or delay disease progression, and may lead to increased patient anxiety, it may avoid the harmful side effects of early intervention and does not preclude palliative therapy if and when symptomatic disease progression occurs. Therefore, quality of life in many men treated with watchful waiting may be superior to those treated with early intervention. Currently, approximately 11% of patients with newly-diagnosed prostate cancer will choose initial watchful waiting, rather than initial active local treatment.[11]

What leads men to choose "watchful waiting " rather than active treatment for prostate cancer depends on a number of factors that influence this decision, including physician recommendation, patient preference, life expectancy, and comorbidities. Diefenbach et al. reported initial results from an ongoing longitudinal investigation examining treatment decision making among 654 men diagnosed with early stage prostate cancer.[12] Of this group, 6% of patients chose watchful waiting. When asked for the most important reason influencing their treatment decision, patients indicated physician recommendation (51%),

advice from friends and family (19%), information obtained from books and journals (18%), and the Internet (7%).

Mclaren et al. followed 113 men who chose watchful waiting after referral to the British Columbia Cancer Agency.[13] Their reason for choosing watchful waiting include patient preference in 37% of the cases, physician recommendation in 42%, decreased life expectancy in 19% and contraindication to radiotherapy in 2%.

Koppie et al. used the CapSURE database to evaluate both advanced and localized prostate cancer patients on watchful waiting and determined that men on watchful waiting were more likely to be older than 75 years of age, have lower serum PSAs, have organ-confined disease, and a total Gleason sum of 7 or less.[14] In agreement with Koppie et al., we noted that men who elected for watchful waiting tended to be older, have lower diagnostic PSA as well as organ-confined disease.

It has been documented that comorbidities often influence the initial decision to choose watchful waiting.[15] However, our results suggest that there is no relationship between a patient's comorbidities and their primary treatment (p=0.6056).

Bauer et al.[16] reported on the hereditary of prostate cancer and found that there was no relationship in the clinical characteristics of a patient's cancer between patients who have a family history as compared to those in whom sporadic prostate cancer occurs. Our results indicated that patients with family history are more likely to choose active treatment rather than watchful waiting (16.4 versus 11.7, $p < 0.0001$). Studies of hereditary prostate cancer have suggested that familial prostate cancer may be more aggressive or equal in aggressiveness as compared to sporadic prostate cancer. But Koysis et al. found that men without a family history of prostate cancer had higher-grade tumors which are associated with a more serious prognosis.[17]

In our study of 1158 watchful waiting patients, 2% died of prostate cancer, and 14.9% died of other causes. In the non-watchful waiting group, the disease-specific and non-specific death rate was 2.4% and 9.1%, respectively. This is similar to the results from Koppie et al. They found that fewer patients

undergoing watchful waiting died of prostate cancer compared to other causes. In their study, disease-specific death was only 3 out of 23 patients (13%).

Our results are also supportive of Johansson's study.[18] In the group of 1158 watchful waiting patients, 23.7% chose a secondary treatment at Year 2, and 44.8% at Year 5 after prostate cancer diagnosis. In the Koppie et al. study population, 39% underwent secondary treatment within the follow-up period with the likelihood of secondary treatment reaching 52.5%.

In our study, the most common form of secondary treatment was hormone treatment (42.6%), followed by external beam radiation therapy (17.2%) and radical prostatectomy (10.9%). This result was similar to that of Koppie et al.[14]

Currently, a policy of watchful waiting with selective active treatment based on predefined criteria of disease progression is feasible.[19] This strategy offers the benefit of an individualized approach based on the demonstrated risk of clinical or biochemical progression over time. Thus, it may decrease the burden of therapy in patients with indolent disease, and provides definitive therapy for those with biologically-active disease. Recently, the characterization of predictive factors for secondary treatment and development of an algorithm to assist decision making has been a "hot topic". In the study by Koppie et al., it is notable that secondary treatment was given more frequently to those with higher serum PSA and to those who were younger at diagnosis. In our study, significant predictors of secondary treatment were age younger than 65 years, diagnosis PSA (≥ 10), and clinical stage ($\geq$ T2). Using only statistically significant variables to predict secondary treatment that were defined in multivariate Cox regression analysis, we developed an equation to calculate the relative risk (RR) of secondary treatment and defined three risk groups (low, intermediate, and high) based on RR of secondary treatment. The Kaplan-Meier survival analysis (Figure II) is supportive of this risk stratification ($p < 0.0001$). Using the equations or tables, clinicians can "plug in " the patient's individual factors to determine risk group. At the time of initial diagnosis or after initial watchful waiting, the risk stratification can help the clinician and patient make decisions about secondary treatment or better tailoring of the patient's follow-up care.

CONCLUSIONS

Men who elected watchful waiting for prostate cancer tend to be older, have lower serum PSA and lower Gleason score. The age at diagnosis, PSA and T-stage are the most significant factors for predicting the likelihood of secondary treatment in watchful waiting patients. The most common form of secondary treatment was hormonal treatment, followed by external beam radiation and radical prostatectomy.

Patients who are younger and had high diagnostic PSA and clinical stage ≥ T2 disease were more likely to undergo secondary treatment. The model based on these three factors may benefit the identification of high-risk patients as candidates for early clinical intervention.

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TABLES

Table I. Type of primary treatment-CPDR Database 1990-2001

	Patients No.	Percentage (%)
Watchful waiting	1158	13.8
Radical prostatectomy	4200	50.1
External beam radiation	2230	26.6
Hormonal	514	6.1
Brachytherapy	284	3.4
Cryotherapy	4	0.1
Total	8390	100.0

Table II. Patients who elected watchful waiting and active local therapy

	Watchful waiting # (%)	Active local therapy # (%)	p value
Total #	1158 (13.8)	7232 (86.2)	
Age at diagnosis			< 0.0001
≤ 65	306 (26.5)	3383 (46.8)	
65.1 – 75	518 (44.8)	3003 (41.6)	
> 75	332 (28.7)	840 (11.6)	
Mean/Median	69.8/70.9	65.6/65.6	< 0.0001
Race			0.0079
Caucasian and others	917 (82.5)	5553 (79.0)	
African American	195 (17.5)	1476 (21.0)	
Clinical stage			< 0.0001
T1	547 (53.6)	2835 (41.3)	
T2	425 (41.7)	3547 (51.7)	
T3 + T4	48 (4.7)	477 (6.9)	
Diagnostic PSA			< 0.0001
≤ 4	235 (23.2)	1162 (16.7)	
4-10	498 (49.3)	3482 (50.1)	
≥10	278 (27.5)	2301 (33.1)	
Mean/Median	15.1/6.4	15.3/7.1	< 0.0001
Highest biopsy Gleason sum			< 0.0001
≤ 4	429 (41.1)	1603 (23.8)	
5 – 6	394 (37.8)	2876 (42.6)	
7	122 (11.6)	1190 (17.6)	
8 – 10	99 (9.5)	1077 (16.0)	
Family history			< 0.0001
No	1023 (88.3)	6043 (83.6)	
Yes	135 (11.7)	1189 (16.4)	
Comorbidity			0.6056
None	476 (41.1)	2962 (41.0)	
1	429 (37.1)	2770 (38.3)	
≥ 2	253 (21.8)	1500 (20.7)	
Death			< 0.0001
Alive	963 (83.2)	6402 (88.5)	
Disease specific death	23 (2.0)	175 (2.4)	
Died of other causes	172 (14.8)	655 (9.1)	

Table III. Watchful waiting patients with and without secondary treatment

	Secondary treatment # (%)	No secondary treatment # (%)	p value (Chi square test)
Total #	453 (39.1)	705 (60.9)	
Age at diagnosis			0.0002
≤ 65	148 (32.7)	158 (22.5)	
65.1 – 75	196 (43.3)	322 (45.8)	
> 75	109 (24.0)	223 (31.7)	
Mean/Median	68.8/70.0	70.5/71.6	0.0004
Race			0.0044
Caucasian and others	346 (78.5)	571 (85.1)	
African American	95 (21.5)	100 (14.9)	
Clinical stage			< 0.0001
T1	192 (45.9)	355 (59.0)	
T2	197 (47.1)	228 (37.9)	
T3 + T4	29 (7.0)	19 (3.1)	
Diagnostic PSA			< 0.0001
≤ 4	62 (14.5)	173 (29.7)	
4-10	217 (50.7)	281 (48.2)	
≥10	149 (34.8)	129 (22.1)	
Mean/Median	18.6/7.4	12.5/5.8	< 0.0001
Highest biopsy Gleason sum			0.5034
≤ 4	164 (39.7)	265 (42.0)	
5 – 6	154 (37.3)	240 (38.0)	
7	49 (11.9)	73 (11.6)	
8 – 10	46 (11.1)	53 (8.4)	
Family history			0.9717
No	400 (88.3)	623 (88.4)	
Yes	53 (11.7)	82 (11.6)	
Comorbidity			0.8491
None	182 (40.2)	294 (41.7)	
1	172 (38.0)	257 (36.5)	
≥ 2	99 (21.8)	154 (21.8)	
Death			0.0762
Alive	389 (85.9)	574 (81.4)	
Disease specific death	10 (2.2)	13 (1.9)	
Died of other causes	54 (11.9)	118 (16.7)	

Table IV. Type of secondary treatment for patients who chose watchful waiting

	#	%
Hormonal treatment	193	42.6
External beam radiation	127	28.0
Radical prostatectomy	111	24.5
Brachytherapy	22	4.9

Table V. Univariate Cox proportional hazards model for predictors of secondary treatment

	Hazards Ratio	95%CI*	p value
Age	0.981	0.970 - 0.991	0.0004
Race			
AA** vs Caucasian and others	1.584	1.261 - 1.990	< 0.0001
Clinical stage			
T2 vs T1	1.503	1.231 - 1.835	< 0.0001
T3+T4 vs T1	2.089	1.413 - 3.088	0.0002
LogPSA	1.353	1.242 - 1.474	< 0.0001
Highest biopsy Gleason sum	1.182	1.102 - 1.267	< 0.0001
Family history	1.029	0.773 - 1.371	0.8447
Number of comorbidities	1.052	0.954 - 1.161	0.3069

*: Confidential interval; **: African American

Table VI. Secondary treatment –free Kaplan-Meier Survival Analysis of primary watchful waiting

	Patients #	% 2 years ± SE	% 5 years ± SE	p Value (log rank test)
Total #	1158	76.3 ± 1.3	55.2 ± 1.7	
Age at diagnosis				0.0002
≤ 65	306	71.2 ± 2.7	44.9 ± 3.3	
65.1 – 75	518	76.0 ± 1.9	56.1 ± 2.6	
> 75	332	81.1 ± 2.2	6.3 ± 3.1	
Race				< 0.0001
Caucasian and others	917	77.0 ± 1.4	57.5 ± 1.9	
African American	195	70.2 ± 3.4	42.2 ± 4.4	
Clinical stage				< 0.0001
T1	547	78.5 ± 1.8	59.7 ± 2.5	
T2	425	72.0 ± 2.3	48.0 ± 2.9	
T3 + T4	48	58.2 ± 7.4	33.1 ± 7.8	
Diagnosis PSA				< 0.0001
≤ 4	235	84.6 ± 2.4	71.9 ± 3.4	
4-10	498	72.8 ± 2.1	48.0 ± 2.8	
≥10	278	66.3 ± 3.0	34.0 ± 3.7	
Highest biopsy Gleason sum				0.0002
≤ 4	429	78.5 ± 2.0	59.7 ± 2.6	
5 – 6	394	76.5 ± 2.2	50.1 ± 3.3	
7	122	72.6 ± 4.2	55.8 ± 5.3	
8 – 10	99	65.2 ± 5.2	40.2 ± 6.6	
Family history				0.8464
No	1023	76.3 ± 1.4	55.4 ± 1.8	
Yes	135	76.5 ± 3.8	54.0 ± 5.3	
Comorbidity				0.7842
None	476	76.4 ± 2.0	55.9 ± 2.6	
1	429	73.4 ± 2.2	54.1 ± 2.9	
≥ 2	253	81.0 ± 2.6	55.9 ± 3.8	

Table VII. Multivariate Cox proportional hazards model for predictors of secondary treatment

	Parameter	Hazards Ratio	95%CI*	p value
Age at diagnosis	- 0.037	0.963	0.950 - 0.977	< 0.0001
LogPSA	0.355	1.427	1.275 - 1.596	< 0.0001
Clinical stage				
T2 vs T1	0.274	1.315	1.043 - 1.658	0.0205
T3+T4 vs T1	0.479	1.615	0.991 - 2.632	0.0543

*: Confidential interval.

Table VIII. Risk groups of secondary treatment and secondary treatment-free survival rates at 2, 5, 7 years after diagnosis

Risk group	Risk of secondary treatment	Patients #	Secondary treatment #	Secondary treatment-free survival rates (%)		
				2 - year	5 - year	7 - year
Low	0.04 – 0.13	251	62	86.3	72.9	65.4
Intermediate	0.14 – 0.19	332	142	71.9	48.3	46.7
High	0.19 – 0.92	331	194	62.8	34.0	23.8

FIGURES

Figure I. Secondary treatment-free survival rate in watchful waiting patients

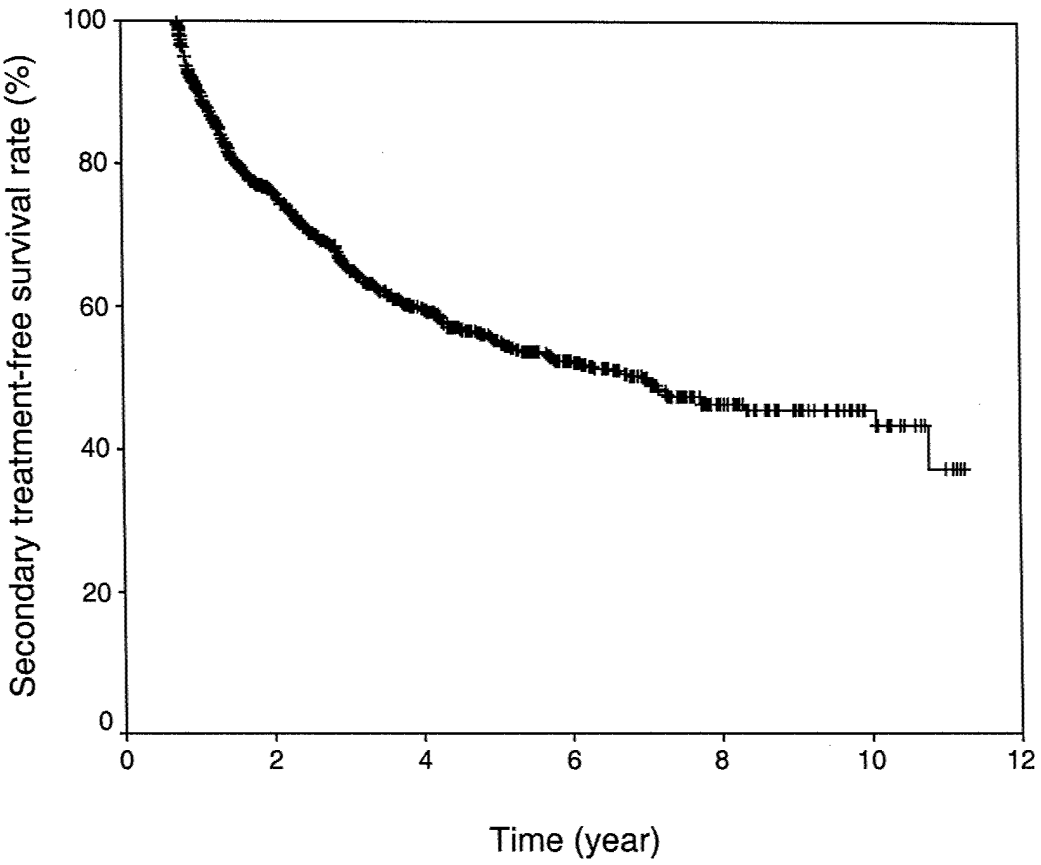
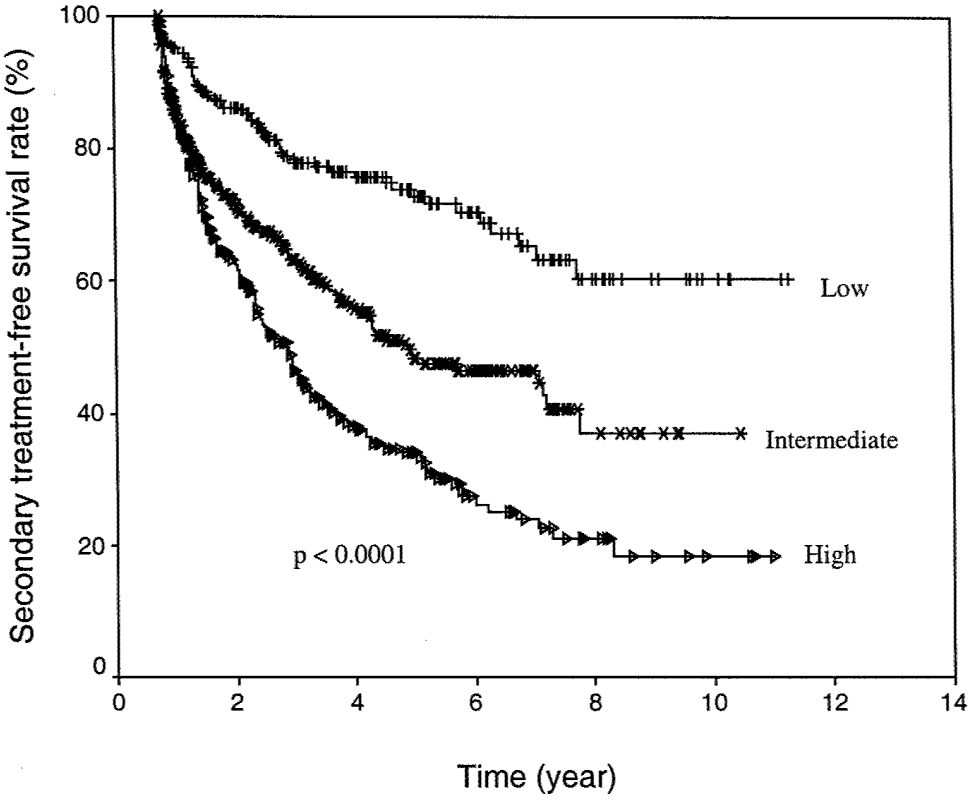


Figure II. Secondary treatment-free survival group in watchful waiting patients stratified by risk group



LEGENDS

Table I. Type of primary treatment-CPDR database 1990-2001

Table II. Patients who elected watchful waiting and active local therapy

Table III. Watchful waiting patients with and without secondary treatment

Table IV. Type of secondary treatment for patients who chose watchful waiting

Table V. Univariate Cox proportional hazards model for predictors of secondary treatment

Table VI. Secondary treatment-free Kaplan-Meier Survival Analysis of primary watchful waiting

Table VII. Multivariate Cox proportional hazards model for predictors of secondary treatment

Table VIII. Risk groups of secondary treatment and secondary treatment-free survival rates at 2, 5, 7 years after diagnosis

Figure I. Secondary treatment-free survival rate in watchful waiting patients

Figure II. Secondary treatment-free survival group in watchful waiting patients stratified by risk group

Appendix 2 (To be submitted to J Urol)

TEMPORARY-DEFERRED THERAPY (TDT) (WATCHFUL WAITING) IN LOW RISK LOCALIZED PROSTATE CANCER IN MEN UNDER AGE 70 IN THE PSA ERA: RESULTS OF THE DEPARTMENT OF DEFENSE (DOD) CENTER FOR PROSTATE DISEASE RESEARCH (CPDR) NATIONAL DATABASE

Corey A. Carter[1], Timothy Donahue[1,2,11], Leon Sun[1], Hongyu Wu[1], David G. McLeod[1,10], Christopher Amling[1,3], Raymond Lance [1,4], John Foley[1,5], Wade Sexton[1,6], Leo Kusuda[1,7], Andrew Chung[1,8], Douglas Soderdahl[1,9], Stephen Jackman[1,2], Judd W. Moul[1,10]

1. Center for Prostate Disease Research (CPDR), Department of Surgery
Uniformed Services University of the Health Sciences,Bethesda, MD 20814

2. Department of Urology, National Naval Medical Center, Bethesda, MD

3. Department of Urology, San Diego Naval Medical Center, San Diego, CA

4. Urology Service, Dept. of Surgery, Madigan Army Medical Center, Tacoma, WA

5. Urology Service, Dept. of Surgery, Brooke Army Medical Center, San Antonio, TX

6. Department of Urology, Wilford Hall AF Medical Center, Lackland AFB, TX

7. Department of Urology, Portsmouth Naval Medical Center, Portsmouth, VA

8. Department of Urology, Malcolm Grow AF Medical Center, Andrews AFB, MD

9. Urology Service, Dept. of Surgery, Eisenhower Army Medical Center, Augusta, GA

10. Urology Service, Dept. of Surgery, Walter Reed Army Medical Center, Washington, DC

Requests for reprints/correspondence:
Dr. Timothy Donahue
Center for Prostate Disease Research
1530 East Jefferson Street
Rockville, MD 20852
Telephone: (240) 453-8951
Fax: (240) 453-8912
Email: tdonahue@cpdr.org

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Key Words: localized prostate cancer, watchful waiting, prostate-specific antigen, young men

ABSTRACT

BACKGROUND: Due to the long natural history of prostate cancer, watchful waiting or deferred therapy has traditionally been viewed as an acceptable strategy for the management of prostate cancer in older men. The routine use of PSA testing has resulted in a stage migration with diagnoses frequently made in younger men with more localized disease. The strategy of deferred management has been infrequently reported in this group of patients. We undertook an analysis of the Department of Defense (DoD) Center for Prostate Disease Research (CPDR) Multicenter Research Database to identify younger men diagnosed during the past decade who elected watchful waiting or deferred therapy as their primary treatment strategy for low/intermediate risk prostate cancer.

MATERIALS AND METHODS: A query of the CPDR database was performed to identify men electing watchful waiting as their initial treatment strategy who met the following criteria at the time of diagnosis: date of diagnosis between January 1991-December 2001, age ≤ 70, Gleason sum ≤ 6 with no Gleason pattern 4, no more than 3 cores positive on biopsy, clinical stage $\leq$ T2, and PSA ≤ 20. We analyzed the likelihood of remaining on watchful waiting, the factors associated with progression to secondary definitive therapy, and the influence of co-morbidities on that decision.

RESULTS: 313 men were identified who met the criteria for analysis. Median length of follow-up was 3.8 years. Median age at diagnosis was 65.4 years (range 41-70). Ninety- eight (31%) men have remained on watchful waiting, while 215 (69%) have proceeded to secondary therapy. Of those who underwent secondary treatment, 57.3% and 73.2% elected to do so within the first 2 and 4 years after diagnosis, respectively. The median PSA doubling time was 2.5 years for those who progressed to therapy; those who remained on watchful waiting had a median

doubling time of 25.8 years. For patients electing secondary treatment, the type of therapy treatment they underwent was associated with the number of patient co-morbidities ($p = 0.012$). Patients with fewer co-morbidities were more likely to choose radical prostatectomy or brachytherapy.

CONCLUSION: Even carefully selected patients under age 70 who initially elect watchful waiting in the PSA era have a 57.3% chance of progressing to definitive treatment in the first 2 years after diagnosis and a 73.2% chance within 4 years. Patients with faster PSA doubling times and higher clinical stage disease (T2b or T2c) were statistically more likely to abandon the strategy of watchful waiting in favor of seeking definitive therapy. While the number and type of major co-morbidities did not predict whether patients would progress to secondary therapy, it did influence the type of definitive therapy ultimately chosen. This treatment strategy may be better termed Temporary Deferred Therapy (TDT) in the PSA era.

INTRODUCTION

Prostate cancer is the most common solid tumor in United States males and is the second leading cause of cancer death.[1] Since the introduction of the prostate-specific antigen (PSA) screening test in the late 1980s and an increase in public awareness of the disease that occurred in the early 1990s, there has been a marked stage and age migration to a preponderance of clinically localized disease and younger age at the time of diagnosis.[2-4] Over two-thirds of men now have localized disease at initial diagnosis and optimal management of clinically localized prostate cancer remains controversial. The traditional treatment options for younger men diagnosed with clinically localized prostate cancer have focused on definitive therapy such as radical prostatectomy or radiation therapy. Watchful waiting or deferred therapy has been utilized as a management strategy primarily in older men who were felt to not have sufficient life expectancy to benefit from more aggressive therapy. In both prospective and retrospective studies, there is some indication that patients with localized prostate cancer who choose watchful waiting may have no loss in life expectancy and that radical treatment may be initially avoided.[8-11] Albertsen et al found that men with low-grade prostate cancer treated conservatively were not expected to have any decrease in life expectancy.[11] There is inadequate data describing watchful waiting in young men with low-grade, low-stage prostate cancer diagnosed during the PSA era to suggest whether this same treatment strategy of deferred therapy can be successfully applied to a younger population of patients. It may be possible to safely follow some men expectantly without immediate treatment and the attendant risks associated with definitive therapy. The goal of watchful waiting or deferred therapy in this cohort of young men would be to detect disease progression and move the patient on to definitive therapy when cure is still possible.

It is estimated that up to one-third of patients identified to have prostate cancer will have low volume disease (less than 0.5 cm^3) that has no poorly differentiated elements (Gleason sum 6 or less). Work performed by Epstein and colleagues has helped to identify criteria predictive of small volume cancers in men with nonpalpable tumors[12]. If the PSA density was less than 0.15 ng/ml per cm^3 and no adverse pathologic findings were present at the time of prostate biopsy, 79% of men had cancers which were small volume (0.5 cm^3 or less), organ confined, and not high grade. Epstein defined the favorable criteria on needle biopsy as Gleason sum 6 or less, no more than 3 cores positive for cancer, and no more than 50% involvement of any core with cancer. Conversely, in men who had a higher PSA density (> 0.15 ng/ml/cm^3), adverse pathologic findings (Gleason 7 or higher, more than 2 cores involved, or >50% involvement of any core), 83% of men had higher volume disease, non-organ confined tumors, or high-grade disease at radical prostatectomy[12]. Using these needle biopsy criteria, it is possible to identify men who have a high likelihood of having low-grade, low volume prostate cancer in whom watchful waiting or deferred therapy might be a reasonable option.

The goal of this cohort study was to identify and describe the natural history of younger men diagnosed with prostate cancer with lower risk features during the PSA era who elected watchful waiting or deferred therapy as their initial treatment strategy, and to identify the factors associated with the decision to proceed to definitive therapy.

MATERIALS AND METHODS

The clinical information and follow-up in this study have been collected as part of the DoD CPDR Tri-Service Multicenter Prostate Disease Research Database as described previously by Sun et al.[16] Briefly, standardized data collection forms for prostate biopsy, registration, staging, watchful waiting, surgery, radiation treatment, hormonal treatment, cryotherapy, follow-

up, and necropsy have been developed and were used. Data was collected and entered by physicians and data managers, then maintained in a relational database using MS Access software as the front end and Oracle software as the back end. The CPDR Database has been approved by the Uniformed Services University Research Administration, Institutional Review Board (IRB) as well as the IRBs of all participating military hospitals. The original protocol in use from 1991 to 1998 did not require patients to sign a formal informed consent document. However, between 1998 and 1999, the IRBs of all sites required patient informed consent to participate. All data entered prior to 1998-1999 (exact date varies by institution) without gaining the patients' informed consent was allowed to be maintained; however, no new information on existing living patients or new enrollees was entered without consent after these dates.

The data query for this study was performed in July 2002. At this time, the overall database contained 345,954 clinical records (i.e., TRUS/biopsy, staging, watchful waiting, follow-up, etc.) on 15,063 patients. Of these, 2,074 (13.8%) had selected watchful waiting as their initial treatment between Jan 1, 1991 and Dec 31, 2001 with complete information on progression of the disease. We modified our selection criteria of patients who elected watchful waiting as their primary treatment strategy to identify those patients who were felt to be the most ideal candidates for deferred therapy adapting the criteria developed by Epstein et al.[12] The goal of these selection criteria was to identify those patients who were felt to have low-grade, low-stage disease at the time of diagnosis and who were also considered to be potential candidates for definitive therapy, such as radical prostatectomy or radiation therapy. These patients had the option of pursuing any type of therapy for their prostate cancer and were not hindered in our equal-access military health care system due to cost/insurance considerations. Patients older than age seventy and those with more advanced disease were purposefully excluded from analysis to

minimize the influence of age and aggressiveness of disease on the decision to pursue watchful waiting. Inclusion criteria for this analysis were a date of diagnosis between January 1991 and December 2001, age ≤ 70, Gleason sum ≤ 6 with no Gleason pattern 4, no more than 3 cores positive on biopsy, clinical stage ≤ T2, and PSA ≤ 20 at the time of diagnosis. Table 1 provides the CPDR Sites total number of watchful waiting cases included in this study and the percentage of these cases of their entire enrolled cohort during the study interval. The discrepancy between the number of patients undergoing watchful waiting and those reviewed in this analysis is due to the preponderance of older patients or those with higher grade disease managed with this strategy of watchful waiting.

The data fields analyzed for this study included patient's age at diagnosis, ethnicity/race, clinical stage at diagnosis, diagnosed prostate-specific antigen (PSA) value, biopsy Gleason sum, number of positive biopsy cores, family history of prostate cancer in a first or second degree relative, and if patients were receiving treatment for symptomatic benign prostate hyperplasia (BPH). Vascular disease risk factors and concurrent co- morbidities at diagnosis were analyzed as independent and collective risk factors for progression to secondary treatment. Co-morbidities analyzed for this review included coronary artery disease, cerebral vascular accident, renal insufficiency, obstructive pulmonary disease, diabetes mellitus, concurrent malignancy, or other systemic disease. Patient co-morbidities were divided into three separate groups for analysis: those having no co-morbidities, patients having 1 co-morbidity, and patients having 2 or more co-morbidities at the time of diagnosis. Additionally, histological grading on repeat biopsies, PSA doubling time, and the type of secondary definitive treatment were also analyzed.

PSA doubling time (Dt) was calculated using the assumption that PSA changes with time in an exponential manner once prostate cancer has been diagnosed.[16-19] All patients with at least

two PSAs in the database were used to calculate doubling time in a regression analysis to determine the slope of the exponential curve. PSA doubling time was calculated on 241 patients with a median number of PSA entries used of 3 (range of 2- 28). Greater than 90% of the 241 patients had a least 3 PSA entries.

Demographics and clinical characteristics were compared between patients who remained on the watchful waiting protocol and those who underwent secondary treatment using chi-square and Fisher's exact test. These factors were further tested using a log- rank method. Additionally, a multivariate Cox proportional hazards regression model was used to assess the predictors of secondary treatment in the total watchful waiting cohort. Of the patients who proceeded to definitive treatment a chi-square analysis was utilized to compare the patient's number of co-morbidities to the choice of secondary treatment elected. Free from secondary treatment curves were calculated using the Kaplan-Meier (KM) method. The KM curves were further stratified by both the patient's PSA Dt, and patient's clinical stage.

RESULTS

Three hundred thirteen patients met the selective inclusion criteria of this analysis, namely being younger men with low-grade, early-stage prostate cancer diagnosed during the PSA era. Table 2 shows the demographics and clinical features of the 313 watchful waiting patients included in the study. The mean and median follow-up time in these cases were 4.2 years and 3.8 years respectively (range from 0.5 to 10.5) after initial diagnosis. Sixty-six percent of the patients were diagnosed prior to 1997. Median age at diagnosis was 65.4 years (range 41-70). Almost one-quarter of the men electing deferred therapy were under age sixty at the time of diagnosis. Two-thirds of these patients were Caucasian, nearly a quarter were African-American, and the remaining nine percent were Asian, Hispanic, or Filipino. Two-thirds of patients had non-

palpable disease at the time of diagnosis; the distribution according to clinical stages is as follows: cT1a/b (5.8%), cT1c (59.7%), cT2a (23%), cT2b (7%), and cT2c (4.5%). The median PSA at diagnosis was 5.1 ng/ml with a range of 0.5-20 ng/ml. Eighty-seven percent of men had a PSA level less than 10 ng/ml at diagnosis with 20.4% having an initial PSA less than 4 ng/ml. As an inclusion criterion, no patient had a Gleason sum greater than 6 and no patient had Gleason pattern 4 in any biopsy core. The median Gleason sum was 5. Nearly two-thirds of patients (63.6%) had only one biopsy core positive at diagnosis, 23.3% had two cores positive, and 13.1 % had three cores positive. During the period of analysis there were 23 deaths in the entire cohort of patients. Two of these deaths were related to prostate cancer, four were related to co-morbid illness, and seventeen were due to other or unknown causes. Three patients developed metastatic prostate cancer.

Factors that may possibly influence the decision to remain on watchful waiting were analyzed and are tabulated in Table 3. Family history of prostate cancer in a first or second-degree relative was positive in 19.5% of patients in the entire cohort of men electing watchful waiting. Nearly a fifth (18.2%) of patients were undergoing active therapy for BPH at the time of diagnosis. Vascular disease risk factors, i.e. smoking history, hypertension, and hyperlipidemia, were positive in 51.1 %, 45%, and 16.9% of men respectively. The prevalences of co-morbidities selected for this analysis were as follows: coronary artery disease (18.8%), cerebral vascular accident (5.1 %), renal insufficiency (3.8%), chronic obstructive pulmonary disease (8.6%), diabetes mellitus (8.6%), systemic disease (1.6%), and concurrent malignancy (16.9%).

Repeat prostate biopsy was only performed in seventy-seven (24.6%) of the patients electing to pursue watchful waiting. The decision to perform a repeat prostate biopsy was made by the urologist caring for the patient and its timing was scheduled according to the surgeon's

preference. Only 24% of repeat biopsies identified an upgrade in Gleason's sum from the initial score; 61 % remained unchanged and 14% experienced a decrease in the Gleason's sum. PSA doubling times were calculated and stratified as follows: less than 2 years (22%), 2-5 years (17.6%), 5-10 years (10.2%),10-20 years (3.2%), 20-50 years (3.5%), and greater than 50 years (20.4%).

Table 4 shows univariate analysis of the demographic and clinical characteristics of the two cohorts in this analysis, namely those patients who remained on watchful waiting and those who elected to proceed with definitive therapy after an initial trial of deferred therapy. Under univariate analysis, significant factors which positively affected the decision to move to secondary treatment were the patient's age ($p = 0.029$), clinical stage ($p = 0.0002$), patients not receiving treatment for BPH ($p = 0.031$), and PSA doubling time ($p < 0.0001$). The finding of the same or an increased Gleason's sum on repeat prostate biopsy was also a significant univariate risk factor for progression to secondary treatment ($p=0.028$). The PSA at diagnosis, number of positive cores, race, and number of vascular and co-morbid risk factors were not associated with the progression to secondary therapy. Table 5 demonstrates Kaplan-Meier estimates for patient's ability to remain free from secondary treatment. The 2 year and 4 year estimates are shown and are stratified by age, clinical stage, PSA doubling time, diagnoses PSA, race, family history, and number of co-morbidities. The long rank p Values are shown which demonstrated both clinical stage and PSA doubling time both being statistically significant (< 0.001). Table 6 shows the multivariate analysis conducted using the categorical data, which found the significant predictors of secondary treatment to be the PSA doubling time and clinical stage.

Table 7 describes the type of treatment elected by the 215 who moved on from watchful waiting. The median time to definitive treatment was 9.6 months. Table 8 compares the number

of co-morbidities at the time of diagnosis with the choice of secondary treatment elected by these patients. Patients with fewer co-morbidities were more likely to elect radical prostatectomy or brachytherapy; those with two or more co-morbidities were more likely to undergo external beam radiation therapy (p=0.012).

Figure 1 is a Kaplan-Meier graph demonstrating the likelihood of a patient remaining free from treatment with time. By two years 57% of men had proceeded to secondary therapy and at four years this number approaches 74%. If a patient remained on watchful waiting after four years there was little probability of moving to definitive therapy. Figures 2 and 3 are representative Kaplan-Meier curves stratified by doubling time and the patient's clinical stage. Patients with the fastest PSA doubling times ($\leq$ 2 years and 2-5 years) and those with palpable disease (cT2a and cT2b/c) more often elected to abandon watchful waiting in pursuit of definitive treatment.

DISCUSSION

Watchful waiting has been proposed as a reasonable treatment strategy of localized prostate cancer in patients with less than a 10 year life expectancy.[8] In both prospective and retrospective studies, there is indication that patients with localized prostate cancer who choose watchful waiting may have no loss in life expectancy and that deferred therapy may be reasonable to initially avoid radical treatment.[8-11] Albertsen et al found in a retrospective analysis of the Connecticut tumor registry that men aged 65 to 75 years with conservatively treated low-grade prostate cancer can expect to incur no loss of life expectancy. In comparison, men with higher-grade tumors (Gleason scores 5 to 10) experienced a progressively increasing loss of life, anywhere from 4-8 years with higher Gleason sum tumors II. Their cohort of men was followed in the era prior to PSA testing and a substantial number of men were over age 70 at

the time of diagnosis. There is no data available looking at watchful waiting in those men who would otherwise be considered excellent candidates for definitive therapy but who opted to pursue a strategy of deferred therapy. We analyzed the CPDR database to identify a selective cohort of younger men with low-grade, early-stage prostate cancer diagnosed during the PSA era who, in general, have a greater than 10-year life expectancy and who elected to pursue watchful waiting as their primary treatment. Despite having quite favorable disease characteristics, the vast majority of these men opted to proceed with definitive therapy within four years of their diagnosis of prostate cancer. The key message is that PSA use has changed the traditional concept of watchful waiting from life-long deferred definitive therapy to temporary deferred local therapy for the majority of men who initially select it.

Koppie et al[13] used the CaPSURE database to evaluate both advanced and localized prostate cancer patients on watchful waiting and determined that men on watchful waiting ~ were more likely to be greater than 75 years old, have lower serum PSAs, have organ-confined disease, and have a total Gleason score of 7 or less. In their group there was a 52% likelihood of secondary treatment within five years. Zietman et al[14] retrospectively reviewed 199 records of men with localized disease whom had a median age of 71. This study similarly showed a 57% chance of patients proceeding to treatment in five years, and that therapy was usually triggered by increases in PSA. These previous series on watchful waiting demonstrate the traditionally accepted strategy of watchful waiting in the older patient with an anticipated survival of less than ten years. By limiting our analysis to younger men with low- to moderate-grade disease under the age of seventy, we have attempted to exclude the majority of patients who elected and remained on watchful waiting due to their advanced age or more aggressive disease and have attempted to evaluate the epidemiology and effectiveness of deferred therapy as a primary treatment strategy

in a younger group of men. By choosing watchful waiting, these men elected to pursue an initial conservative strategy for managing their prostate cancer and thereby avoid the possible side effects associated with surgery or radiation therapy. Despite selecting for men with tumor characteristics that would appear favorable for watchful waiting, we found that 53% of these younger men abandoned this strategy by two years. However, if a patient remained on watchful waiting for four years, there was little likelihood of progressing to secondary therapy. This is the first study to show that watchful waiting in contemporary younger men is temporary deferred local therapy dictated primarily by PSA.

As with other investigators[14,15,17,18], we found that PSA doubling time is the most significant factor associated with secondary treatment. Nam et al[18] suggested that a rapidly rising PSA occurs in up to 31% of patients on watchful waiting. We found similar results with 22% of the patients in our analysis having a PSA doubling time of less than two years and an additional 17.6% of patients having doubling times between two and five years. These patients with the fastest PSA doubling times were found to have an 81% chance of leaving watchful waiting to undergo secondary, definitive treatment. This may reflect an initial underestimation of the patient's tumor burden or the presence of occult higher grade cancer, suggesting the patient may not have been an ideal candidate for watchful waiting.

While we found that age was a factor in the choice to pursue secondary treatment by univariate analysis, when we analyzed the patient's age in both the log-rank and the Cox analysis, we found it was not a predictor of secondary treatment for this cohort. In these younger men, PSA, not age, drives the decision for secondary therapy.

Similar to Koppie et al[13], we found clinical stage was a highly significant factor for predicting which patients will undergo secondary treatment. Those with palpable disease (cT2b

or cT2c) were most likely to abandon watchful waiting as their primary treatment strategy. This may reflect a greater burden of tumor than was initially estimated at the time of diagnosis. However, in contrast to Koppie et al[12], the initial PSA level at diagnosis was not a predictor of secondary treatment. A likely reason why our results differ from Koppie et al[12] is because we only included those patients whose initial PSA was less than 20 ng/ml; no exclusionary PSA criteria were used in Koppie et al's review. For patients in our review, the initial PSA at the time of diagnosis was not a predictor of progression to secondary therapy, however, the PSA doubling time was highly predictive.

Epstein et al[21] demonstrated that men undergoing watchful waiting who underwent repeat biopsies showed little evidence of the prostate cancer grade worsening over the short term. He implied that tumor differentiation is not expected to worsen during a one-and-a-half to two-year period after initial biopsy. In his study, all 77 men had either an increase or stability in their Gleason sum. In our review, 77 patients received repeat biopsies and the decision to undertake the biopsy was made by the attending urologist and patient. Sixty-one percent of patients had the same and 24% had an increase in their Gleason sum on repeat needle biopsy. If a higher proportion of the cohort had undergone repeat biopsy, this factor may have been more predictive of secondary treatment. However, the fact that only one quarter of men had a repeat biopsy underscores the powerful clinical use of PSA change in this setting.

Bratt et al[22] reported on hereditary of prostate cancer and found there was no relationship between the clinical characteristics of patients who have a positive family history compared to those with sporadic prostate cancer. Our analysis found similar results in that a positive family history did not statistically influence the decision to progress to secondary therapy.

The database does not include why patients initially elected watchful waiting, but much is known about their initial co-morbidities and vascular disease risk factors. It has been documented that co-morbidities often influence the initial decision to choose watchful waiting.[9,11] Our study attempted to understand how co-morbidities affect decisions in secondary treatment. It is conceivable that if a patient has multiple co-morbidities both the surgeon and patient would be less likely to opt initially for aggressive therapy and that these co-morbidities could influence the decision to proceed to secondary treatment. Our results, however, suggest there is no relationship between a patient's co-morbidities and the ability to remain free from secondary treatment. No single co-morbidity, nor even a number of co-morbid illnesses, appeared to affect the decision to move to definitive therapy. Again, PSA drove this decision, not concurrent illness. However, we did identify that the number of co-morbid illnesses did statistically influence the choice of secondary therapy elected. Those patients with no co-morbidities were most likely to pursue radical prostatectomy or brachytherapy; those with two or more co-morbidities chose external beam radiation therapy.

This study provides a better understanding of patients who are under the age of 70, and have clinically localized prostate cancer. There are many factors that influence both patients and surgeons decision to choose watchful waiting as well as many factors that influence their decision to go on receive secondary treatment. Our review of carefully selected, younger men with low grade, low stage prostate cancer found that these men were unlikely to pursue this strategy as a long-term treatment. Instead of watchful waiting, this approach may better be termed "temporary deferred therapy (TDT)" in this population in the PSA era. The initial PSA level, age, race, family history, number or type of co-morbidities did not predict the progression to secondary treatment. The most predictive factors for a patient abandoning watchful waiting

and progressing to definitive therapy were the PSA doubling time and the initial clinical stage. Those patients with faster doubling times (less than five years) and palpable tumor burden (T2b or T2c) were statistically most likely to move to secondary treatment.

The next analysis to be performed in this review is to compare the outcomes of the 215 patients who started on a course of watchful waiting and moved to definitive therapy as compared to men who elected immediate, definitive treatment. This study is underway and should provide insight into whether temporary deferred therapy (TDT) or watchful waiting is a reasonable management strategy for young men during the PSA era. Our review suggests it is important to closely follow patients during the first four years after diagnosis with serial PSA measurements. Those with faster PSA doubling times or higher clinical stage disease may be less than ideal candidates for this strategy and may be served better with immediate therapy due to the high likelihood of abandoning watchful waiting in the first two years.

CONCLUSIONS

Even carefully selected patients under age 70 with low grade, low stage prostate cancer who initially elect watchful waiting in the PSA era have a 57.3% chance of receiving secondary treatment in the first two years after diagnosis and a 73.2% chance in the first four years. Patients who have a PSA doubling time of five years or less or have a clinical stage of T2b or T2c have a 81% and 89% chance of going on to receive secondary treatment respectively. The number of co-morbidities does not predict whether or not patients will seek secondary treatment, but does affect the type of secondary treatment chosen. Those with no co-morbid illnesses were most likely to pursue radical prostatectomy or brachytherapy; those with two or more co-morbidities most often received external beam radiation therapy. Rather than "watchful waiting" this strategy is better termed "temporary deferred therapy (TDT)" in younger PSA-era men.

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Table 1. Participating CPDR Sites, Total Watchful Waiting Cases in the Database between 1991 and 2001.

Abbreviation	Full Name	Total WW Cases	WW Cases for this study	% of WW/Total
BAMC	Brooke Army Medical Center	180	32	17.8
EAMC	Eisenhower Army Medical Center	69	11	15.9
MAMC	Madigan Army Medical Center	275	22	8.0
MGMC	Malcolm Grow Medical Center	107	11	10.3
NMCP	Naval Medical Center Portsmouth	155	37	23.9
NMCSD	Naval Medical Center San Diego	175	48	27.4
NNMC	National Naval Medical Center	325	26	8.0
WHMC	Wilford Hall Medical Center	184	36	19.6
WRAMC	Walter Reed Army Medical Center	607	90	14.8
OVERALL	CPDR National Database	2077	313	15.1

Table 2. Demographic factors in 313 WW patients between 1991-2001 in this study

	Number	Percent (%)
Dx ERA		
1991	7	2.2
1992	15	4.8
1993	18	5.8
1994	38	12.1
1995	31	9.9
1996	54	17.3
1997	46	14.7
1998	36	11.5
1999	35	11.2
2000	26	8.3
2001	7	2.2
Age		
<60	75	24.0
60.1-65	99	31.6
65.1-70	139	44.4
Race		
Caucasian	209	66.8
African American	76	24.3
Other	28	8.9
Clinical stage		
T1a/b	18	5.8
T1c	187	59.7
T2a	72	23.0
T2b	22	7.0
T2c	14	4.5
Diagnosis PSA		
<= 4.0	64	20.4
4.1–6.0	102	32.6
6.1–10.0	108	34.5
10.1-20.0	39	12.5
Biopsy Gleason		
<=4	85	27.2
5	73	23.3
6	119	38.0
TSTG*	36	11.5
Number of Positive Cores		
1	199	63.6
2	73	23.3
3	41	13.1
Metastatic Disease		
Total	3	0.9
Death		
Total	23	7.3
Related to Prostate Ca	2	0.6
Related to Co-Morbidity	4	1.3
Other Causes	7	2.2
Unknown Causes	10	3.1

*:Sample size was insufficient to be able to score a Gleason

Table 3. Watchful Waiting factors in 313 patients between 1991-2001

	Number	Percent (%)
Family History		
No	252	80.5
Yes	61	19.5
Treatment of Symptomatic BPH		
No	256	81.8
Yes	57	18.2
Vascular Disease Risk Factors		
Smoking	160	51.1
Hypertension	141	45.0
Hyperlipidemia	52	16.6
Comorbidities		
CAD	59	18.8
CVA	16	5.1
Renal Insufficiency	12	3.8
COPD	27	8.6
Diabetes	49	15.6
Systemic Disease	5	1.6
Other Cancers	53	16.9
Repeat Biopsies		
Upgrade in Gleason Sum	19	6.1
No Change in Gleason Sum	47	15.0
Downgrade in Gleason Sum	11	3.5
Total	77	24.6
PSA Doubling Time (years)*,#		
<2	69	22.0
2-5	55	17.6
5.1-10	32	10.2
10.1-20	10	3.2
20.1-50	11	3.5
>50	64	20.4
Total	241	77.0

*Median doubling time 4.6 years.

All available PSA data was used with >90% of the patients having 3 or more entries.

Table 4. Univariate analysis of factors associated with Secondary Treatment in 313 WW patients between 1991-2001.

	WW no Secondary Tx (percent)	WW with Secondary Tx (percent)	p Value
Age			0.029
<=60	21 (21.4)	54 (25.1)	
60.1-65	23 (23.5)	76 (35.4)	
65.1-70	54 (55.1)	85 (39.5)	
Clinical Stage			0.0002
T1a/1b	13 (13.3)	5 (2.3)	
T1c	55 (56.1)	132 (61.4)	
T2a	26 (26.5)	46 (21.4)	
T2b	3 (3.1)	19 (8.8)	
T2c	1 (1.0)	13 (6.1)	
Receive Tx for BPH			0.020
No	74 (75.5)	182 (84.7)	
Yes	24 (24.5)	33 (15.3)	
Patients who received repeat biopsy (n=77)			0.031
Increase or same Gleason	15 (71.4)	51 (91.1)	
Decrease in Gleason	6 (28.6)	5 (8.9)	
PSA doubling time (n=241)			< 0.0001
<2	8 (8.3)	61 (42.1)	
2-5	16 (16.7)	39 (26.9)	
5.1-50	31 (32.3)	22 (15.2)	
>50	41 (42.7)	23 (15.9)	
Dx PSA			0.23
<=4	27 (27.5)	37 (17.1)	
4.1-6	32 (32.7)	70 (32.6)	
6.1-10	30 (30.6)	78 (36.3)	
10.1-20	9 (9.2)	30 (14.0)	
Dx Gleason sum			0.14
<=4	9 (11.0)	10 (5.1)	
5	21 (25.6)	45 (23.1)	
6	24 (29.3)	49 (25.1)	
TSTG	28 (34.1)	91 (46.7)	
Number of positive cores on initial biopsy			0.32
1	60 (61.2)	139 (64.6)	
2	21 (21.4)	52 (24.2)	
3	17 (17.3)	24 (11.2)	
Race			0.36
Caucasian	68 (70.8)	141 (67.8)	
African-American	20 (20.8)	56 (26.9)	
Other	8 (8.4)	11 (5.3)	
Number vascular disease factors per patient			0.79
0	27 (27.6)	58 (27.0)	
1	36 (36.7)	91 (42.3)	
2	27 (27.6)	51 (23.7)	
3	8 (8.1)	15 (7.0)	
Number of comorbidities per patient			0.54
0	51 (52.0)	118 (54.9)	
1	25 (25.5)	60 (27.9)	
>=2	22 (22.5)	37 (17.2)	
Deaths			
Related to Prostate Ca	1	1	
Related to Co-Morbidity	2	2	
Other Causes	5	2	
Unknown Causes	4	6	
Metastatic Disease	0	3	

Table 5. Kaplan-Meier estimates of free from secondary treatment

	Number Pts.	% 2 years +/- SE	% 4 years +/- SE	p Value (log rank test)
All WW Patients	313	42.7 +/- 2.9	26.8 +/- 2.8	
Age				0.1929
<=60	75	38.4 +/- 5.8	28.7 +/- 5.5	
60.1-65	99	40.9 +/- 5.1	15.9 +/- 4.3	
65.1-70	139	44.8 +/- 4.4	32.6 +/- 4.5	
Clinical Stage				< 0.0001
T1a/1b	18	72.2 +/- 10.6	72.2 +/- 10.6	
T1c	187	43.6 +/- 3.7	23.7 +/- 3.6	
T2a	72	44.1 +/- 6.1	31.7 +/- 6.2	
T2b	22	17.9 +/- 8.7		
T2c	14	11.9 +/- 7.5		
PSA doubling time				< 0.0001
<2	64	13.9 +/- 5.6	2.5 +/- 7.1	
2-5	69	45.1 +/- 4.6	21.4 +/- 2.4	
5.1-50	55	80.5 +/- 6.9	61.9 +/- 6.7	
>50	53	74.9 +/- 5.5	56.3 +/- 7.2	
Dx PSA				0.1248
<=4	8	50.0 +/- 17.7		
4.1-6	56	47.2 +/- 6.7	41.1 +/- 6.7	
6.1-10	102	44.3 +/- 5.1	27.3 +/- 5.0	
10.1-15	108	40.4 +/- 4.9	18.9 +/- 4.5	
15.1-20	39	30.6 +/- 7.7	14.5 +/- 6.8	
Race				0.0728
Caucasian	209	44.0 +/- 3.5	29.3 +/- 3.4	
African-American	76	32.6 +/- 5.6	16.6 +/- 5.3	
Other	19	52.6 +/- 11.5	35.5 +/- 13.4	
Family HIstory				0.3817
No	252	43.6 +/- 3.2	27.2 +/- 3.1	
Yes	61	37.3 +/- 6.3	22.1 +/- 6.2	
Number of comorbidities per patient				0.3773
0	169	44.0 +/- 3.9	28.5 +/- 3.8	
1	85	37.1 +/- 5.4	22.4 +/- 5.3	
>=2	59	47.8 +/- 6.8	28.8 +/- 6.7	

Table 6. Cox proportional hazards model for predictors of secondary treatment

Risk of secondary treatment	Hazards Ratio	95% CI	p Value
Clinical Stage			
cT1c vs. cT1a/b	7.077	1.642-30.498	0.0087
cT2a vs. cT1a/b	5.647	1.260-25.302	0.0237
cT2b vs. cT1a/b	9.184	1.933-43.644	0.0053
cT2c vs. cT1a/b	16.400	3.159-85.157	0.0009
PSA Dt			
2-5 vs. <2	0.325	0.202-0.523	<0.0001
5.1-50 vs. <2	0.116	0.063-0.212	<0.0001
>50 vs. <2	0.133	0.073-0.242	<0.0001
Age			
60-65 vs. <60	1.067	0.646-1.762	0.7997
65-70 vs. <60	0.736	0.428-1.268	0.2700
PSA at diagnoses			
4.1-10.0 vs. 0-4.0	1.311	0.751-2.287	0.3410
10.1-20.0 vs. 0-4.0	1.069	0.523-2.184	0.8559
Gleason score			
5 vs. 2-4	1.017	0.613-1.689	0.9477
6 vs. 2-4	1.450	0.914-2.301	0.1148
Number of comorbidities per patient			
1 vs. 0	1.022	0.649-1.610	0.9259
2 vs. 0	0.861	0.516-1.436	0.5658
Family History of CaP			
Yes vs. No	1.376	0.868-2.183	0.1748
Race			
Caucasian vs. African American	1.131	0.726-1.763	0.5861

Table 7. 215 Patients that underwent Secondary Treatment

	Number of Pts.	Percent
Types of Treatment		
Radical Prostatectomy (RP)	104	48.4
External Beam Irradiation (XRT)	57	26.5
Brachytherapy (B)	39	18.1
Androgen deprivation	13	6.0
Cryosurgery	2	0.9
Time to treatment (months)		
Mean	15.0	
Median	9.6	
Range	6-81	

Table 8. Co-morbidities vs. Types of Treatment

	RP (percent)	B (percent)	XRT (percent)	p Value
Number of co-morbidities per patient				0.012
0	67 (64.4)	21 (53.9)	21 (36.8)	
1	25 (24.0)	12 (30.8)	20 (35.1)	
>=2	12 (11.5)	6 (15.4)	16 (28.1)	

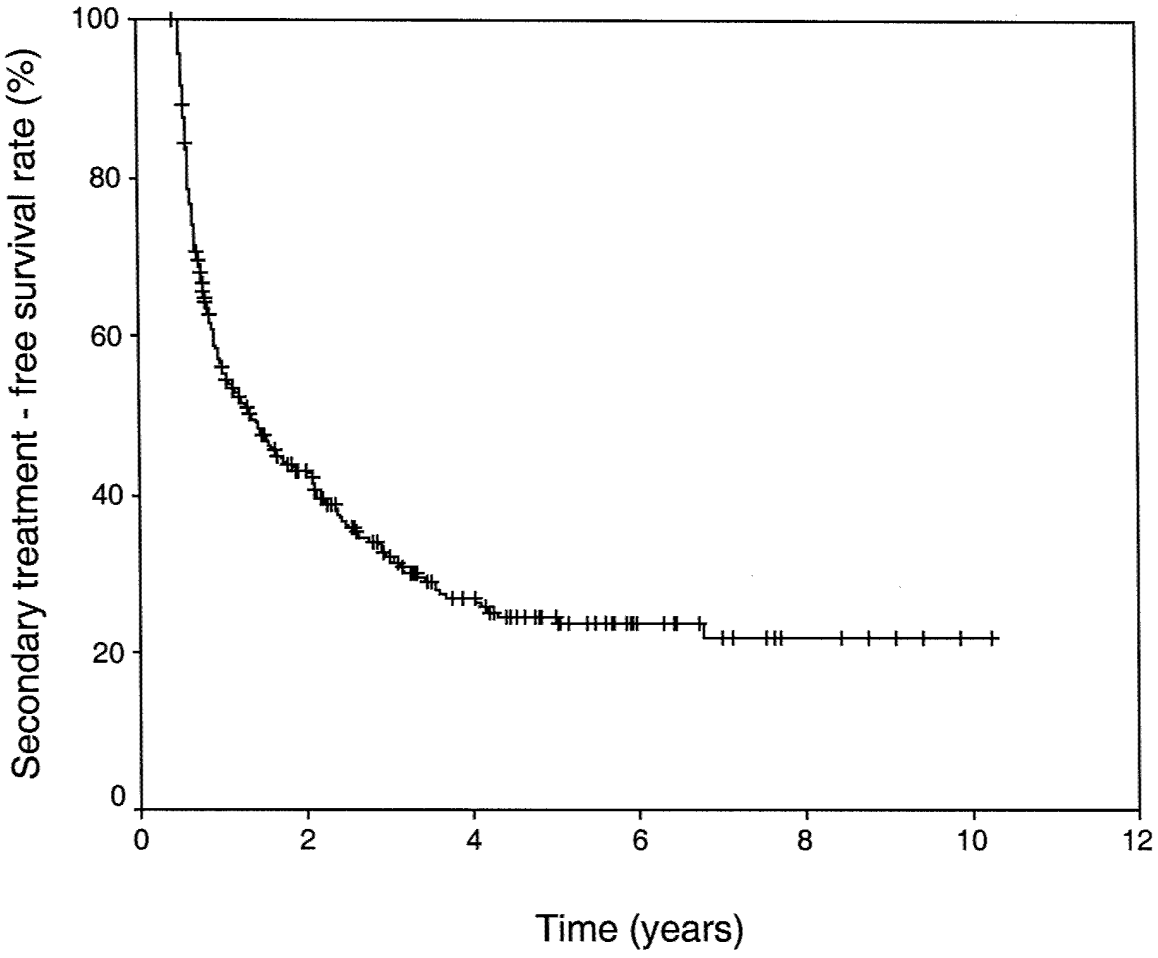

Figure 1. Kaplan-Meier free from secondary treatment curve in 313 WW patients

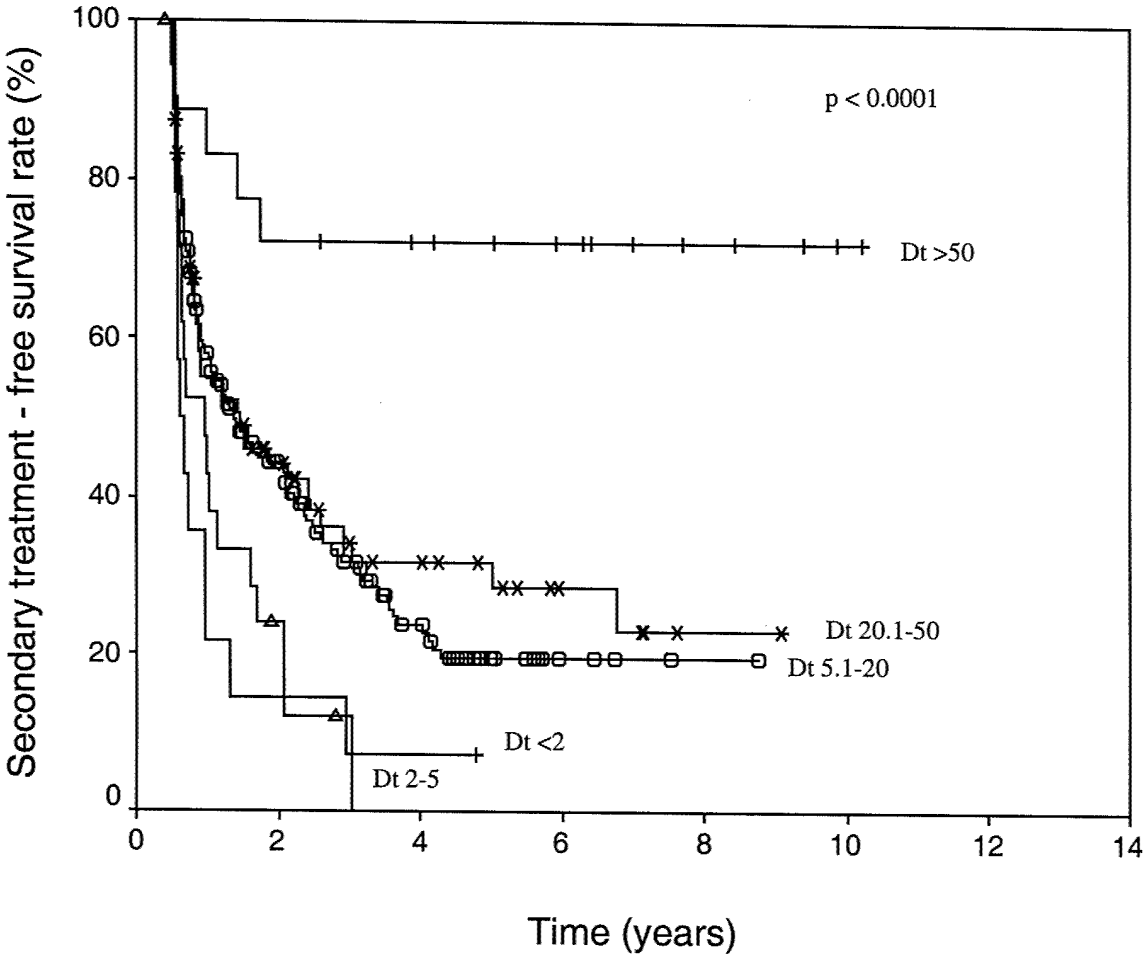

Figure 2. Kaplan-Meier free from secondary treatment curve stratified by patient's PSA doubling time

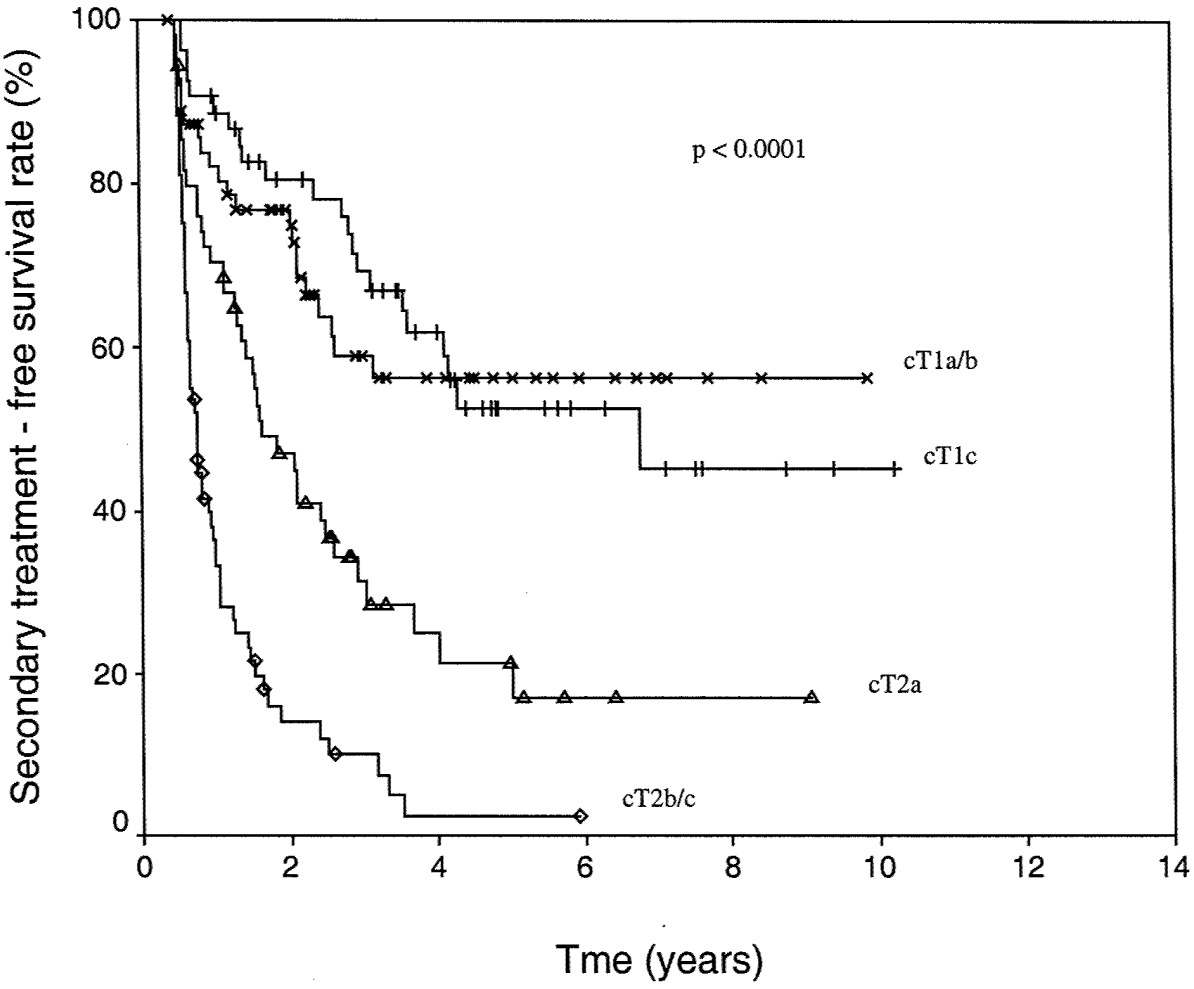

Figure 3. Kaplan-Meier free from secondary treatment curve stratified by clinical stage

Apendix 3 (Accepted as moderated poster by AUA 2003 and submitted to Journal of National cancer Institute 2003)

SURROGATE MARKER FOR PROSTATE CANCER SPECIFIC MORTALITY FOLLOWING RADICAL PROSTATECTOMY OR RADIATION THERAPY

Anthony V. D'Amico, MD, PhD[1]; Judd Moul, MD[2]; Peter R. Carroll, MD[3]; Leon Sun, MD[2]; Deborah Lubeck, PhD[3]; Ming-Hui Chen, PhD[4]

[1]Department of Radiation Oncology

Brigham and Women's Hospital and Dana Farber Cancer Institute

[2]Department of Urology, Center for Prostate Disease Research

Walter Reed Army Medical Center

[3]Department of Urology, University of California, San Francisco

[4]Department of Statistics, University of Connecticut

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Please send Correspondence to:

Anthony V. D'Amico, MD, PhD Tel: **(617)-732-7936**

Brigham and Women's Hospital Fax: **(617)-975-0912**

Department of Radiation Oncology email: **adamico@lroc.harvard.edu**

75 Francis Street, L- 2 Level, Boston, MA 02215

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ABSTRACT

Purpose: This study evaluated a recently proposed hypothesis that a short post-treatment prostate-specific antigen doubling time (PSA DT) may serve as a surrogate for prostate cancer specific mortality (PCSM).

Methods: Two multi-institutional databases containing baseline, treatment and follow up information on 8,669 men treated with either surgery (N = 5918) or radiation (N = 2751) from 1988 to 2002 for clinical stage T1c-4NxMo prostate cancer comprised the study cohort. The PSA DT interval selected for study as a possible surrogate of PCSM corresponded to the maximum time interval that minimized the difference in the estimates of PCSM and all cause mortality (ACM) following PSA failure. Prentice's criteria require that the surrogate was a prognostic factor and that the treatment utilized did not alter the time to PCSM following achievement of the surrogate. These criteria were tested using Cox regression.

Results: The maximum value of the PSA DT interval that minimized the difference in the estimates of PCSM and ACM following PSA failure was < 3 months. A PSA DT < 3 months was a significant predictor of both time to PCSM ($p_{Cox} < 0.0001$) and time to ACM ($p_{Cox} < 0.0001$) following PSA failure. The treatment received was not a significant predictor of time to PCSM ($p_{Cox} = 0.37$) or ACM ($p_{Cox} = 0.67$) following PSA failure for patients with a PSA DT < 3 months.

Conclusion: These data provide evidence to support a post-treatment PSA DT < 3 months as a surrogate for PCSM following surgery or radiation therapy.

INTRODUCTION

While essentially always found in conjunction with an asymptomatic patient, prostate-specific antigen (PSA) failure following initial therapy with either radical prostatectomy (RP) or external beam radiation therapy (RT) is considered treatment failure. Therefore, PSA failure is often used as the trigger to initiate secondary therapy.[1] However, whether PSA failure given time will translate into prostate cancer specific mortality (PCSM), particularly for men with competing causes of mortality remains unknown.[2]

Therefore, as an initial step toward identifying those patients in whom PSA failure is likely to translate into death from prostate cancer, investigators have tried to define the predictors of the time to documentation of distant failure (i.e. positive bone scan) following PSA failure. From these investigations[3-7] one post-treatment clinical parameter, a short post-treatment PSA doubling time (PSA DT) was consistently found to be a significant predictor of time to distant failure following PSA failure.

The next step was aimed at identifying predictors of time to PCSM following PSA failure. Specifically, a study[8] evaluating the determinants of time to PCSM following PSA failure in RT managed patients found that patients with a short post-treatment PSA DT had estimates of PCSM and all cause mortality (ACM) following PSA failure that were nearly identical. These results confirmed the findings of a previous study[9] regarding the prognostic significance of a short post treatment PSA DT. Taken together these two studies provided evidence to support the hypothesis that a short post-treatment PSA DT was able to identify patients with PSA failure following RT who were at high risk for PCSM.

In the current study, baseline, treatment and follow up data on 8,669 men treated with either RP or RT at multiple institutions throughout the United States were compiled and used to assess whether a short post-treatment PSA DT following either RP or RT can serve as a surrogate for PCSM.

METHODS

Patient Selection and Treatment

Two multi-institutional data bases containing baseline, treatment and follow up information on 8,669 men treated with either RP (N = 5918) or RT (N = 2751) between 1988 and 2002 for clinical stage T1c-4NxMo prostate cancer comprised the study cohort. These 2 databases included patients from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE)[10] and the Center for Prostate Disease Research (CPDR).[11] In order to be eligible for study entry, surgically managed patients were permitted to have received up to 3 months of neoadjuvant androgen suppression therapy (AST) given that the 5 year results of a randomized trial[12] has shown no significant impact on PSA outcome from adding 3 months of neoadjuvant AST to RP. The median age (range) of the surgical and radiation managed patients at the time of initial therapy was 64.5 (34.3 – 96.8) and 71.1 (43.7 – 92.8) years respectively. The pre-treatment clinical characteristics of all patients stratified by the treatment received are shown in Table 1.

Staging

In all cases staging evaluation involved a history and physical examination including a digital rectal exam (DRE), serum PSA, and a transrectal ultrasound guided (TRUS) needle biopsy of the prostate with Gleason score histologic grading.[13] The prostate biopsy was performed using an 18 gauge Tru-Cut needle (Travenol Laboratories, Deerfield, Illinois) via a trans-rectal approach. Prior to 1996 patients generally had a computerized tomographic scan of the pelvis and bone scan. After 1996 patients with both a pre-treatment PSA level less than 10 ng/ml and a biopsy Gleason score of 6 or less did not generally undergo radiologic staging due to the < 1% chance that these studies would reveal metastatic disease.[14] The clinical stage was obtained from the DRE findings using the 2002 American Joint Commission on Cancer (AJCC) staging system.[15] Radiologic and biopsy information were not used to determine clinical stage.

All PSA measurements were made using the Hybritech (San Diego, Calif), Tosoh (Foster City, Calif), or Abbott (Chicago, Il) assays.

Follow up

The median follow up for the entire study cohort of 5918 and 2751 surgically and radiation managed patients was 7.1 (0.5 – 14.3) and 6.9 (0.8 – 14.5) years respectively using the first day of treatment as time zero. Prior to PSA failure which was defined using the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus criteria,[16] patients generally had a serum PSA measurement and DRE performed every 3 months following RT for 2 years then every 6 months for 3 additional years then annually thereafter. The median follow up defining the date of PSA failure as time zero for the 611 and 840 RP and RT managed patients who have experienced PSA failure was 4.1 (0.3 – 11.8) and 3.8 (0.3 – 12.0) years respectively. Overall, there were 154 deaths, 110 of which were from prostate cancer. The determination of the cause of death was made using death certificates.

STATISTICAL METHODS

Calculation of the PSA DT

Unlike surgically managed patients, radiation managed patients do not necessarily achieve an undetectable PSA (< 0.2 ng/ml), but often nadir at a finite value typically < 1.0 ng/ml within 2 years following RT. Therefore, in order to be certain the magnitude of the PSA DT would be the same for surgical and radiation managed patients who experienced the same absolute rises in PSA, the nadir PSA value was subtracted from the post radiation PSA's before the DT calculation was performed. The PSA DT was calculated assuming first order kinetics and

using a minimum of 3 PSA values each separated in time by a minimum of 3 months and each having a rise of > 0.2 ng/ml. Therefore, the minimum PSA value that was used to calculate the PSA DT needed to be > 0.2 ng/ml for all study patients.

Selection of the Candidate Surrogate

The value of the PSA DT interval (e.g. < 12 or < 6 or < 3 months) selected to be tested as a possible surrogate for PCSM using Prentice's criteria[17] corresponded to the maximum PSA DT interval that minimized the difference in estimates of PCSM from the cumulative incidence plots[18] and estimates of ACM from the Kaplan Meier plots[19] for patients treated using surgery or radiation therapy. An additional test to identify the candidate surrogate was also performed. Specifically, the marginal proportion of the variation in PCSM explained (mPVE)[20] using different values of the PSA DT interval was calculated to ensure that the PSA DT interval identified based on the comparison of the estimates of PCSM and ACM also maximized the mPVE value.

Prentice's Criteria

Prentice's criteria[17] required that the surrogate was a prognostic factor and that once a patient had achieved the surrogate endpoint, the time to PCSM following the achievement of the surrogate was independent of the treatment received. A Cox regression analysis[21] whose endpoint was time to PCSM following PSA failure was used to test these criteria. The predictors evaluated included the candidate surrogate, and treatment (surgery versus radiation) for patients who achieved the candidate surrogate. Age (continuous) at the time of PSA failure was also included in the Cox model that evaluated time to ACM following PSA failure. It is important to

note that for these 2 Cox regression analyses, achievement of the surrogate endpoint and sustaining PSA failure defined as 3 consecutive rises in PSA[16] were synonymous.

In order to add further evidence to support or refute a lack of treatment effect on the time to PCSM following PSA failure for patients who achieved the surrogate endpoint an additional measure of treatment effect was performed. Specifically, the partial proportion of the variation in the PCSM data and ACM data explained (pPVE)[20] by the adding treatment received to the Cox model containing the candidate surrogate was also calculated.

Whether the initial treatment received was a significant predictor of time to PCSM following PSA failure after adjusting for the value of the PSA DT for patients who did not achieve the candidate surrogate was also tested using Cox regression. Specifically, for the Cox model evaluating time to PCSM following PSA failure, the indicators included the post treatment PSA DT (continuous) and treatment (surgery versus radiation). Similarly, the impact of treatment received on predicting time to ACM following PSA failure adjusting for both the value of the PSA DT and age at the time of PSA failure was also evaluated using Cox regression for patients who did not achieve the candidate surrogate. The specific factors evaluated for this analysis included age (continuous) at the time of PSA failure, PSA DT (continuous) and treatment (surgery versus radiation).

For the Cox regression analyses, time zero was taken as the day of PSA failure, which was defined as the midpoint between the PSA nadir and first rise.[16] For all analyses, the assumptions of the Cox model were tested and met. For the purpose of illustration, estimates of

PCSM and ACM following PSA failure stratified by whether the patient had achieved the candidate surrogate, and by the treatment received were graphically displayed. Comparisons of survival were made using the log rank test.

RESULTS

Selecting the Candidate Surrogate

The maximum value of the PSA DT interval that minimized the difference in the estimates of PCSM and ACM following PSA failure for all patients was < 3 months. Of the 611 surgically managed and 840 radiation managed pts who sustained PSA failure, 12% and 20% had a PSA DT < 3 months respectively as shown in Figures 1 and 2. In addition, the mPVE value was maximized for a PSA DT less than 3 months. Specifically, these values were 11%, 12%, and 14% for a PSA DT less than 5, 4, and 3 months respectively for surgically managed patients and the corresponding values were 7%, 7.4% and 9% for radiation managed patients.

Application of Prentice's Criteria

As shown in Table 2 and illustrated in Figures 1 and 2, a PSA DT < 3 months was a significant predictor of both time to PCSM ($p_{Cox} < 0.0001$) and time to ACM ($p_{Cox} < 0.0001$) following PSA failure. In addition, for patients with a PSA DT < 3 months, treatment received was not a significant predictor of time to PCSM ($p_{Cox} = 0.37$) or time to ACM ($p_{Cox} = 0.67$) following PSA failure using a Cox regression multivariable analysis. Specifically, as shown in Figures 1 and 2, the differences in the estimates of PCSM ($p_{log\ rank} = 0.38$) and ACM ($p_{log\ rank} = 0.34$) following PSA failure were not significantly different for patients treated with either surgery or radiation. The lack of impact of the treatment received on the time to PCSM and ACM following PSA failure for patients with a PSA DT < 3 months was further supported by the pPVE results. Specifically, the additional information provided by adding treatment to the Cox model that contained the predictor of a PSA DT < 3 months regarding time to PCSM and time to ACM following PSA failure were much less than 1% corresponding to pPVE values of 0.06%

and 0.01% respectively.

For patients with a PSA DT of 3 months or more, there were significant differences in the distribution of PSA DT ($p_{\text{Chi Square}} < 0.0001$) and age at the time of PSA failure ($p_{\text{Chi Square}} < 0.0001$) between surgery and radiation managed patients as shown in Table 3. In addition, for these patients significant differences existed for both time to PCSM ($p_{\text{log rank}} = 0.0002$) and ACM ($p_{\text{log rank}} < 0.0001$) following PSA failure for patients treated with surgery versus radiation as noted in Figures 1 and 2 respectively. However, when adjusting for the differences in the distribution of value of the PSA DT and age at the time of PSA failure using a Cox regression analysis, treatment was no longer a predictor of time to PCSM ($p_{\text{Cox}} = 0.28$) or time to ACM ($p_{\text{Cox}} = 0.12$) following PSA failure as shown in Table 2.

DISCUSSION

Once initiated, randomized trials comparing surgery and radiation for patients with localized prostate cancer often take greater than a decade from inception to reporting due to the long natural history of the disease following primary therapy. Therefore, in order to achieve answers more quickly regarding efficacy of new treatments, risk groups[22] and nomograms[23] have been developed to identify patients for entry on to randomized clinical trials who are at high risk of PSA recurrence following surgery or radiation therapy based on pre-treatment,[22-23] post-treatment[24] parameters or both[25] However, not all patients who are at high risk for PSA recurrence, recur and an even smaller proportion die of the disease due to competing causes of mortality.

The identification of a surrogate for PCSM for surgical and radiation managed patients would greatly impact randomized clinical trial design and reporting when comparing treatment efficacy between (e.g. RP vs RT) or within these modalities (e.g. RT to a dose of 70 vs 78 Gy). Specifically, a smaller sample size and a significantly shorter follow up could be utilized if the study was powered based on the surrogate endpoint as compared to survival, providing answers regarding relative treatment efficacy more rapidly. Moreover, identification of a surrogate for PCSM would identify the optimal group of patients following primary local treatment failure to select for study of novel systemic therapies.

Recent data[8] has provided evidence to support the hypothesis that a short PSA DT following radiation therapy may serve as surrogate for PCSM. Therefore, the purpose of this study was to validate or refute this hypothesis by applying Prentice's criteria[17] for a surrogate

endpoint to a large multi-institutional database where patients could have been treated with surgery or radiation therapy.

The results of this study provided evidence to support a PSA DT < 3 months as a surrogate for PCSM. Specifically, a PSA DT < 3 months was a significant predictor of both time to PCSM ($p_{Cox} < 0.0001$) and time to ACM ($p_{Cox} < 0.0001$) following PSA failure for patients treated using surgery or radiation. For patients with a PSA DT < 3 months, the treatment received was not a significant predictor of time to PCSM ($p_{Cox} = 0.37$) or ACM ($p_{Cox} = 0.67$) following PSA failure as shown in Figures 1 and 2 respectively. In particular, the additional information provided regarding the prediction of the time to PCSM following PSA failure by adding treatment received to the Cox model that contained a PSA DT < 3 months was only 0.06% (pPVE = 0.06). Taken together these findings satisfied Prentice's criteria for surrogacy.

Patients with a PSA DT of 3 months or more did die of causes other than prostate cancer following PSA failure as noted by the lower overall survival compared to prostate cancer specific survival noted by comparing Figures 1 and 2 for both surgery and radiation managed patients. However, after adjusting for the significantly shorter PSA DT in radiation versus surgically managed patients as shown in Table 3, treatment received was not a significant predictor of the time to PCSM following PSA ($p_{Cox} = 0.28$) as shown in Table 2. Similarly, if both the shorter PSA DT and older age at the time of PSA failure in radiation as compared to surgically managed patients were adjusted for using Cox regression, then treatment received did not predict for time to ACM following PSA failure ($p_{Cox} = 0.12$) as shown in Table 2. The shorter post-treatment PSA DT and the higher median age at the time of PSA failure for radiation as compared to

surgically managed patients noted in Table 3 can be explained by the fact that surgical treatment is generally recommended in younger patients with less advanced disease as can be seen in Table 1. These results suggested that given the value of the post-treatment PSA DT, the time to PCSM following PSA failure can be predicted and is independent of the treatment received providing further support for the overall prognostic significance of the post-treatment PSA DT.

Given that 12% of all surgical and 20% of all radiation managed patients who sustained PSA failure achieved the surrogate endpoint, what are the clinical implications of the results of this study? In practice the results provide evidence to support that these patients are destined to die of androgen insensitive metastatic prostate cancer despite currently available salvage therapies. Specifically, the median survival following PSA failure in patients achieving the surrogate was 6 years as shown in Figure 2. Therefore, patients who achieve this endpoint should be referred for entry on to clinical trials examining new forms of systemic therapy. These patients should also be given the opportunity to start androgen suppression therapy once they are identified. Given that a short PSA DT has been shown to be associated with a short time to distant failure following PSA failure,[3-7] these men are at very high risk for the associated sequelae (e.g. pathologic fracture, spinal cord compression) of metastatic bone disease in a short time interval following PSA failure. Therefore, judicious use of early salvage hormonal therapy could be performed by providing it to men with a PSA DT < 3 months because these men are most likely to derive a benefit in quality of life from prolonging their relatively short symptom free interval.

A few clarifications regarding the possible use of the results of this study to aid in **the**

design of future randomized clinical trials are needed. First, whether a PSA DT < 3 months could serve as a surrogate for PCSM for patients treated with radiation and hormonal therapy or in the setting of radiation or surgery used in conjunction with any other form of systemic therapy would require that the analysis used in this study be performed in that patient cohort. However, this study does provide evidence to support a PSA DT < 3 months as a surrogate endpoint for a trial of surgery versus external beam radiation, or a trial comparing two radiation doses or two surgical techniques (e.g laparoscopic versus open). The currently ongoing trial of prostate brachytherapy versus surgery or the planned trial of brachytherapy with or without supplemental external beam RT may also be able to use a PSA DT < 3 months as a surrogate based on the studies findings. However, rules for clarifying a PSA bounce[26] from PSA recurrence would be needed for patients whose management included brachytherapy.

In brief, following either surgery or radiation therapy in the management of clinically localized or locally advanced prostate cancer, a PSA DT < 3 months served as a surrogate for prostate cancer specific mortality. Patients who achieve the surrogate following surgery or external beam radiation therapy should be given the opportunity to begin hormonal therapy in order to delay the imminent sequelae of metastatic bone disease and then referred for entry on to clinical trials investigating new forms of systemic therapy for this disease.

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Table 1: Percent distribution of the pre-treatment clinical characteristics of the 5918 surgery and 2751 radiation managed patients comprising the study cohort

Clinical Characteristic	Surgery	Radiation	$P_{Chi\text{-}Square}$
PSA 4 ng/ml or less	18%	11%	
PSA > 4 – 10 ng/ml	58%	45%	$p < 0.0001$
PSA > 10 ng/ml	17%	26%	
PSA > 20 ng/ml	8%	19%	
Biopsy Gleason score 6 or less	74%	61%	
Biopsy Gleason score 7	21%	26%	$p < 0.0001$
Biopsy Gleason score 8 – 10	5%	13%	
2002 AJCC Category T1c	40%	32%	
2002 AJCC Category T2a	33%	29%	
2002 AJCC Category T2b	20%	20%	
2002 AJCC Category T2c	4%	8%	$p < 0.0001$
2002 AJCC Category T3a	2%	8%	
2002 AJCC Category T3b	0.1%	2%	
2002 AJCC Category T4	0.1%	1%	
Age < 50	4%	1%	
Age 50 – 59	28%	7%	
Age 60 – 69	55%	37%	$p < 0.0001$
Age 70 – 74	12%	31%	
Age 75 – 79	1%	20%	
Age 80 and over	0.3%	4%	

PSA: Prostate-Specific Antigen

AJCC: Amercian Joint Commission on Cancer

Age: Age at the time of initial therapy

Percentages may not sum to 100 due to rounding

Table 2: Results of the Cox Regression Multivariable Analyses evaluating the overall prognostic significance of the post-treatment prostate specific antigen doubling time (PSA DT) and whether Prentice's criteria[17] are satisfied for a PSA DT < 3 months

Endpoint: Time to Prostate Cancer Specific Death following PSA Failure			
PSA DT < 3 mos vs ≥ 3 mos	< 0.0001	PSA DT (continuous)*	< 0.0001
Treatment 1	0.37	Treatment 2	0.28
Endpoint: Time to All Cause Death Following PSA Failure			
PSA DT < 3 mos vs ≥ 3 mos	< 0.0001	PSA DT (continuous)*	< 0.0001
Treatment 1	0.67	Treatment 2	0.12
Age at PSA failure (continuous)	0.0002	Age at PSA failure (continuous)	< 0.0001

Treatment 1: Surgery is compared to Radiation for patients with a PSA DT < 3 months

Treatment 2: Surgery is compared to Radiation for patients with a PSA DT ≥ 3 months

* The PSA DT is evaluated as a continuous variable for values of 3 months or greater

Table 3: Percent distributions of the age at the time of PSA failure and the post treatment prostate-specific antigen doubling time (PSA DT) for patients with a PSA DT of 3 months or greater stratified by initial treatment received.

PSA DT (months)	Surgery	Radiation	p-value
3 – 5.99	18%	23%	
6 – 11.99	32%	37%	$p < 0.0001$
12 or greater	50%	40%	
Age (years)			
< 50	0.4%	0.2%	
50 – 59	15%	3%	
60 – 69	51%	23%	$p < 0.0001$
70 – 74	22%	31%	
75 – 79	10%	29%	
80 or greater	1.5%	15%	

Percentages may not sum to 100 due to rounding

FIGURE LEGENDS:

Figure 1: Prostate cancer specific survival following PSA failure stratified by treatment received and the value of the post-treatment prostate specific antigen doubling time (PSA DT)

Pairwise log rank p-values:

PSA DT < 3 months (Surgery versus Radiation) $p = 0.38$

PSA DT ≥ 3 months (Surgery versus Radiation) $p = 0.0002$

PSA DT < 3 months vs ≥ 3 months (Surgery) $p < 0.0001$

PSA DT < 3 months vs ≥ 3 months (Radiation) $p < 0.0001$

Figure 2: Overall survival following PSA failure stratified by treatment received and the value of the post-treatment prostate specific antigen doubling time (PSA DT)

Pairwise log rank p-values:

PSA DT < 3 months (Surgery versus Radiation) $p = 0.34$

PSA DT ≥ 3 months (Surgery versus Radiation) $p < 0.0001$

PSA DT < 3 months vs ≥ 3 months (Surgery) $p < 0.0001$

PSA DT < 3 months vs ≥ 3 months (Radiation) $p < 0.0001$

Apendix 4 (Accepted as moderated poster by AUA 2003 and by J Urol for publication)

PRETREATMENT TOTAL TESTOSTERONE LEVEL PREDICTS PATHOLOGIC STAGE IN RADICAL PROSTATECTOMY PATIENTS WITH LOCALIZED PROSTATE CANCER

Jason C. Massengill,[1,2] Leon Sun,[2] Judd W. Moul,[2,3,12] Hongyu Wu,[2] David G. McLeod,[2,3] Christopher Amling,[2,4] Raymond Lance,[2,5] John Foley,[2,6] Wade Sexton,[2,7] Leo Kusuda,[2,8] Andrew Chung,[2,9] Douglas Soderdahl,[2,10] Timothy Donahue,[2,11]

2. Uniformed Services University of the Health Sciences
Bethesda, MD 20814

3. Center for Prostate Disease Research (CPDR)
Department of Surgery
Uniformed Services University of the Health Sciences
Bethesda, MD 20814

4. Urology Service, Department of Surgery
Walter Reed Army Medical Center
Washington, D.C. 20307-5001

5. Department of Urology
San Diego Naval Medical Center
San Diego, CA

6. Urology Service, Dept. of Surgery
Madigan Army Medical Center
Tacoma, WA

7. Urology Service, Dept. of Surgery
Brooke Army Medical Center
San Antonio, TX

8. Department of Urology
Wilford Hall AF Medical Center
Lackland AFB, TX

9. Department of Urology
Portsmouth Naval Medical Center
Portsmouth, VA

10. Department of Urology
Malcolm Grow AF Medical Center
Andrews AFB, MD

11. Urology Service, Dept. of Surgery
Eisenhower Army Medical Center
Augusta, GA

12. Department of Urology
National Naval Medical Center
Bethesda, MD

12. Requests for reprints/correspondence:
Center for Prostate Disease Research
1530 East Jefferson Street
Rockville, MD 20852
Telephone: (240) 453-8951
Fax: (240) 453-8912
Email: JMOUL@CPDR.ORG

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Key Words: testosterone, prostate cancer, radical prostatectomy, stage, predict

Running Title: Pretreatment testosterone predicts pathologic stage

ABSTRACT

PURPOSE: In the past decade, numerous groups have shown low levels of pretreatment serum total testosterone to consistently predict more aggressive disease, worse prognosis, and worse treatment response in patients with metastatic prostate cancer. Prior studies have not demonstrated this same correlation in patients with known localized disease. We sought to rigorously test pretreatment total testosterone levels as a potential staging and prognostic marker in a large cohort of 879 radical prostatectomy patients with localized cancer.

METHODS: We retrospectively reviewed the clinical records of 879 radical prostatectomy patients between January 1, 1986 and June 30, 2002 from nine hospital sites. Nonparametric tests were used to compare the relationship of pretreatment testosterone to other variables. Multivariable logistic regression analysis was used to assess for clinical predictors of extraprostatic disease. Kaplan Meier survival methods and Cox regression analysis were used to assess predictors of biochemical recurrence.

RESULTS: Patients with non-organ confined prostate cancer (pT3-T4) showed significantly lower pretreatment total testosterone levels than those with organ confined cancer (pT1-T2) (Nonparmetric $p = 0.041$). In multivariate analysis, pretreatment total testosterone emerged as a significant independent predictor of extraprostatic disease ($p = 0.046$). Total testosterone was not a significant predictor of biochemical (PSA) recurrence ($p = 0.467$).

CONCLUSIONS: Pretreatment total testosterone was an independent predictor of extraprostatic disease in localized prostate cancer patients. As testosterone decreases, patients have a higher likelihood of non-organ confined disease. Low testosterone was not predictive of biochemical recurrence; however, trends observed dictate study in larger cohorts with mature follow-up.

INTRODUCTION

Since the introduction of the prostate-specific antigen (PSA) screening test, there has been a marked stage migration to a preponderance of clinically localized disease.[1] Over two-thirds of men now have localized disease at initial diagnosis and are candidates for primary local therapy with curative intent.[1] In this new PSA-era with increasing localized disease, the use of radical prostatectomy by urologists has increased dramatically between the mid-1980s and late 1990s.[2] However, urologists are still limited in their pre-operative ability to predict pathologic tumor stage in a reliable manner. To date, clinical stage, tumor grade (biopsy Gleason score) and serum PSA are established pre-operative prognostic markers for pathologic stage.[3] Yet, it has been documented that 30% to 40% of men who undergo RP for clinically organ-confined localized carcinoma of the prostate will have extraprostatic disease or experience disease recurrence.[4] Thus, the need for additional preoperative prognostic markers for patients with clinically localized disease is evident.

In 1941, Huggins et al[5] firmly established a clear association between androgens and prostate cancer. Laboratory studies have revealed that androgens are important for the growth and maintenance of the prostate, for stimulating the proliferation of human prostate cancer *in vitro*, and for producing prostate cancer in rodents.[6] Serum PSA production has also been shown to be androgen dependent at the cellular level.[7] Over a decade ago, a clinical report demonstrated rapid clinical progression of unsuspected cancer after testosterone administration.[8] However, current clinical data on prostate cancer and serum testosterone remains clouded by conflicting studies.

Pretreatment total testosterone in patients with metastatic prostate disease (stage D2) has been investigated by numerous groups over the past two decades. Studies have consistently demonstrated more aggressive disease, worse prognosis, and worse treatment response in patients with low serum total testosterone levels.[9-12] Studies have reported low pretreatment testosterone levels (less than 300 ng/dL) to be significantly associated with shorter progression free survival rates.[9] Ribeiro et al[10] found that low pretreatment testosterone levels result in more aggressive disease and worse prognosis in advanced prostate

cancer. Chen et al[11] found that low testosterone levels were poor prognostic factors for patients undergoing androgen ablation irrespective of tumor grading.

Conversely, in studies on patients with clinically localized prostate cancer, total testosterone levels have not been found to be predictive of stage. In addition, no correlation has been found with known clinicopathological features, such as PSA, tumor volume, prostatic weight, Gleason score or extraprostatic extension.[13-15] Two studies, in particular, have investigated serum total testosterone in small cohorts of men with clinically localized disease treated with radical prostatectomy. Both were unable to demonstrate significant association with total testosterone.[13, 15] Hoffman et al, however, did demonstrate patients with low free testosterone had more aggressive disease.[15]

To confound the situation further, some studies on localized prostate cancer have demonstrated opposite results to the traditional metastatic disease literature. These studies found that high testosterone levels were associated with higher rates of metastatic relapse. Zagars et al[14] found that higher pretreatment total testosterone, especially greater than 500 ng/dL, significantly correlated with metastatic relapse but not PSA recurrence. Gann et al[15] suggested that high testosterone and low sex hormone-binding globulin are associated with a higher risk of prostate cancer. Finally, Imamoto et al[16] found pretreatment total testosterone levels in patients with clinically localized disease were significantly lower than that those patients with stage D2 patients.

Thus, in an effort to clear the incompletely understood association of testosterone with prostate cancer, our objective in this study was to utilize the mature Department of Defense (DoD) Center for Prostate Disease Research (CPDR) Multicenter Research Database to analyze pretreatment testosterone levels in clinically localized prostate cancer patients. We performed a retrospective analysis in a patient population with prostate disease that was predominantly clinically organ confined who were treated with radical prostatectomy and who had pretreatment testosterone data available. We sought to rigorously test pretreatment total testosterone levels as a potential staging and prognostic marker in this large cohort of 879 patients.

MATERIALS AND METHODS

In July 2002, we retrospectively evaluated all clinical and follow up information on patients with prostate cancer treated with radical prostatectomy in the DoD CPDR Tri-Service Multicenter Prostate Disease Research Database between Jan 1, 1986 and June 30, 2002. Our criteria required patients to have serum total testosterone levels that were determined at diagnosis or prior to treatment. Testosterone was not drawn at a specific time and was at the discretion of the treating physician although a testosterone value was a field on the CPDR staging form as an encouraged test in our clinical research. This query revealed 928 patients; 49 were excluded secondary to receiving neo-adjuvant treatment prior to surgery. It was unknown if any patients were on testosterone replacement, however, this would have been a rare occurrence.

The clinical information and follow-up has been collected as part of the DoD CPDR Tri-Service Multicenter Prostate Disease Research Database. Prospective and retrospective comprehensive clinical data has been collected on all consenting patients with prostate cancer. As of January 1, 1994, the data collection was prospective on all new patients with prostate cancer. Similar retrospective data have also been collected on all those treated since 1970 through inpatient and outpatient record reviews and patient interviews. Standardized data collection forms for prostate biopsy, registration, staging, surgery, surgical pathology, radiation treatment, hormonal treatment, cryotherapy, follow-up, and necropsy have been developed and were used. Data was collected and entered by physicians and data managers, then maintained in a relational database. The CPDR Database has been approved by the Uniformed Services University Research Administration Institutional Review Board (IRB), as well as the IRBs of all participating military hospitals.

Pretreatment serum total testosterone levels were recorded in two different concentrations among the nine hospitals using a commercially available radioimmunoassay. Recorded results were in ng/mL and ng/dL with the normal range quoted by the producer as 286 to 1510 ng/dL. For this study, all results were reported in ng/dL.

Radical prostatectomy pathology reports were retrospectively reviewed and histologic analysis performed by standard processing for patients treated before May 1993. After May 1993, the prostates were prospectively evaluated by whole-mount 2.25-mm step sectioning at the Armed Forces Institute of Pathology. Organ-confined prostate cancer (pT1-T2) was defined as a specimen that had no capsular penetration, positive surgical margins, or seminal vesicle or pelvic lymph node involvement. Extraprostatic disease (pT3-T4) was defined as cancer on any inked margin, any capsular penetration, or pelvic lymph node or seminal vesicle involvement.

Histopathologic grading was done according to the World Health Organization (WHO) method of glandular differentiation. The value of grade used in this study was a combination of the WHO and Gleason systems. Gleason grades 2 to 4 or WHO grade well was considered grade well, Gleason grades 5 to 7 or WHO grade moderate was considered moderate, and Gleason grades 8 to 10 or WHO grade poor was considered grade poor. Staging was based on the modified Whitmore-Jewett system and the 1992 TNM classification. Biochemical recurrence of prostate cancer was defined as two successive PSA measurements greater than 0.2 ng/mL.

Non-parametric tests were used to study the relationship of pretreatment testosterone and pathologic stage to other variables in univariate analysis. Multivariable logistic regression analysis assessed the clinical usefulness of pretreatment testosterone and eight other covariates as predictors of pathologic stage. In all analyses, p less than 0.05 was considered to indicate statistical significance. Pathologic stage was a dichotomous categorical variable with two levels (pT1-T2 versus pT3-T4), as were race (black versus not black), and adjuvant treatment (yes versus no). The biopsy and pathologic Gleason (WHO) grade were categorical variables with four levels (2 to 4 (well), 5 to 6 (moderate), 7 (moderate), 8 to 10 (poor)). Clinical stage was a categorical variable with three levels (cT1 versus cT2 versus cT3-T4). Pretreatment total testosterone, creatinine, age, prostatic acid phosphatase (PAP), alkaline phosphatase, and log-transformed prostate-specific antigen (PSA) level entered the model as continuous variables. Kaplan –

Meier survival curves and Cox regression analyses were used to study the relationship of several of these variables to PSA recurrence.

RESULTS

Relationship of total testosterone and other variables to pathologic stage

Table I shows the distribution of the 879 patients with localized prostate cancer treated with radical prostatectomy who had pretreatment testosterone data available for analysis from nine hospital sites. Tables II summarizes the demographic data, pretreatment serum levels of selected tests, clinical stage and biopsy Gleason (WHO) score. Table III provides selected surgical factors, pathologic Gleason (WHO) score, and pathologic stage on the patient cohort.

Table IV shows the mean, median, and range of total testosterone (entered as a continuous variable) in a univariate analysis to each of the stratified covariate groups. Most noteworthy from this table, and shown in Figure I, is the relationship of pretreatment total testosterone levels with pathologic stage. Patients with non-organ confined pathological stage showed significantly lower serum total testosterone than those with organ confined cancer (Nonparmetric $p = 0.041$). Increasing pretreatment prostatic acid phosphatase (PAP) was associated with statistically significant increases in serum total testosterone ($p = 0.044$). There was a trend toward declining testosterone values with increasing age; however, these values were not significantly different ($p = 0.103$). Pretreatment total testosterone values did not significantly differ when compared to race, pretreatment alkaline phosphatase, pretreatment creatinine, pretreatment PSA, clinical stage, biopsy Gleason (WHO) score, and pathologic Gleason (WHO) score. Though not significant, another interesting trend was as patients' serum PSA increased, their mean total testosterone levels decreased ($p = 0.269$).

Table V shows a multivariate logistic regression model with testosterone and eight other covariates; four factors entered as statistically significant independent predictors of extraprostatic disease. Pretreatment total testosterone level was an independent significant predictor of pathologic stage ($p = 0.046$). The other predictors were log value of pretreatment PSA levels ($p < 0.0001$), biopsy Gleason

(WHO) score (p = 0.0160), and pretreatment prostatic acid phosphatase levels (p = 0.0287). Age, race, clinical stage, alkaline phosphatase, and creatinine were not statistically significant predictors of pathologic stage (not shown).

Relationship of total testosterone and other variables to biochemical recurrence

At the time of this analysis, the mean follow-up for the 879 patients was 37.7 months; 12 men died during follow-up period with no PSA or clinical recurrence. The following end-point events were observed during the follow-up period: 129 (14.7%) patients had PSA recurrence, 22 (2.5%) patients had distant metastatic relapse (D2 disease), and 4 (0.5%) patients died a prostate cancer related death. Table VI shows univariate analysis data from selected factors using the Kaplan-Meier survival methods to predict biochemical recurrence-free survival. The five groups of pretreatment serum total testosterone levels did not show significant differences in their rates of PSA recurrence (p = 0.467). Pretreatment PSA, pretreatment PAP, race, pathologic Gleason (WHO) score, and pathologic stage were all significant predictors of PSA recurrence; all other covariates were statistically insignificant. With evidence in past literature, we also performed a survival analysis on two groups of testosterone utilizing the clinical cut-off point of 300 ng/dL. Figure II demonstrates that it is not a significant predictor of PSA recurrence (p = 0.347). In multivariable Cox regression analysis (not shown), treatment age, pathologic stage, and race were independent predictors of PSA recurrence. Pretreatment testosterone was not a significant predictor of PSA recurrence (p = 0.119).

DISCUSSION

Total testosterone predicts pathologic stage

The major finding of our study is that patients with clinically localized prostate cancer treated with radical prostatectomy have a statistically significant correlation between pretreatment total testosterone levels and pathologic stage. This correlation held up in multivariable analysis; pretreatment total testosterone emerged as an independent predictor of extraprostatic disease. As serum testosterone

decreases, patients have a higher likelihood of non-organ confined disease (pT3-T4). These results indicate that low pretreatment total testosterone may be a marker for more aggressive disease in clinically localized prostate cancer. However, confounding variables of circadian rhythm of secretion, influence of body-mass index, and interassay variability for serum testosterone herald caution to these retrospective results. A controlled prospective study would seem indicated based on our provocative results.

Patients with metastatic prostate cancer and testosterone levels less than 300 ng/dL have been shown to have more aggressive disease, worse prognosis, and worse treatment response than those with normal or higher serum total testosterone.[9-12] Prior to our study, no group had shown the same association between total testosterone and clinically localized prostate cancer. In 1994, Monda et al[13] performed a similar study as we performed. They found that total testosterone has no clinical value in predicting pathologic stage. Their cohort consisted of only 90 radical prostatectomy patients. In 2000, Hoffman et al[15] also performed a similar study to ours. They found that lower levels of pretreatment free testosterone were associated with more aggressive disease. However, they did not find an association with total testosterone levels. Their prostatectomy cohort consisted of only 57 patients. In our study, total testosterone was a predictor of extraprostatic disease in univariate and multivariate analyses. Our findings, when compared to the prior two studies with similar cohorts, were discovered secondary to the power of our large cohort of patients available for analysis when compared to the other relatively small cohorts of patients.

This study found opposite results of several recent studies that have proposed high levels of testosterone were associated with worse disease.[14-16] These studies relied on clinical staging and the primary treatment was radiation and/or hormonal therapy. The actual status of disease in their patients was not confirmed by pathologic assessment of radical prostatectomy. Thus, the conclusions about pathological stage and biochemical recurrence were not possible or not as reliable.

While we show that low testosterone was an independent predictor of pathologic stage, there are a number of limitations to our study. As previously noted, testosterone has a circadian rhythm of secretion

and we did not control the time of the assay. Other factors such as body-mass index influence testosterone levels and we were unable to control for this. We did not know the status of men regarding androgen replacement therapy although this was likely a rare event in this cohort. Despite these limitations, the results are provocative and should prompt more controlled study.

The mechanism for this testosterone effect remains unclear. Some groups have speculated low testosterone levels are secondary to the chronic disease status and are the consequence of advanced disease rather than a causative factor.[12] Most recently, Zhang et al have studied total and free testosterone before and after radical prostatectomy in 164 patients finding low testosterone associated with high grade disease.[21] Furthermore, levels were higher after prostate removal suggesting that prostate cancer itself inhibited androgen levels. Other groups have speculated low serum testosterone results in the growth of more androgen-independent carcinoma cells.[10] Still others have proposed that a central mechanism may be involved. Miller et al[18] noted increased testosterone levels as well as other serum hormone levels after radical prostatectomy. It has been suggested this occurs because the prostate and/or prostate cancer cells may produce inhibin, or some other substance, that has a centrally acting inhibitory role (negative feedback) on the hypothalamic pituitary axis.[7,19] When the prostate and/or the cancer is removed, this inhibitory substance is also removed allowing testosterone levels to increase.[20] Low testosterone association with pathologic stage may be related to the biology of the disease or possibly be circumstantial or coincidental. Although we did not see an association between total testosterone and age, race, and clinical stage, it is possible that low testosterone was a surrogate of other factors that relate to pathologic stage.

Clearly, combining PSA, clinical stage and preoperative biopsy grade and quantitative biopsy histology increases the pre-operative ability to predict pathologic stage.[3] Pretreatment total testosterone levels might be used by clinicians in the future assessment and management of men with localized prostate cancer. Future risk assessment models and nomograms may want to consider total testosterone levels, particularly those using neural network analysis considering a multitude of prognostic factors.

Total testosterone does not predict biochemical recurrence

It is generally accepted that worse tumor grade, extraprostatic disease, and PSA are significant predictors of biochemical recurrence of prostate cancer in patients treated with radical prostatectomy. The data from our 879 patient cohort demonstrated these same covariates to be statistically significant independent predictors of PSA recurrence. Although not significant, we found that low total testosterone, especially less than 300ng/dL, showed a trend as a predictor of PSA recurrence (Table VI, Figure II). Very large clinical trials are likely needed to ascertain the prognostic value of testosterone level in relation to biochemical or clinical recurrence. This is an area that awaits further study, but, as suggested by our data, might be promising.

CONCLUSIONS

Patients with localized prostate cancer treated with radical prostatectomy have a statistically significant correlation between pretreatment total testosterone levels and pathologic stage. In multivariable analysis, total testosterone emerged as an independent predictor of extraprostatic disease. As serum testosterone decreases, patients have a higher likelihood of non-organ confined disease (pT3-T4). Low total testosterone level was not predictive of biochemical recurrence; however, trends observed dictate study in larger cohorts with mature follow-up.

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Table I. Participating CPDR sites and total radical prostatectomy cases from the National Database between 1986 to 2002 for this study

Abbreviation	Full Name	RP cases for this study	Percent (%)
BAMC	Brooke Army Medical Center	124	14.1
EAMC	Eisenhower Army Medical Center	19	2.2
MAMC	Madigan Army Medical Center	19	2.2
MGMC	Malcolm Grow Medical Center	34	3.9
NMCP	Naval Medical Center Portsmouth	9	1.0
NMCSD	Naval Medical Center San Diego	77	8.7
NNMC	National Naval Medical Center	7	0.8
WHMC	Wilford Hall Medical Center	200	22.8
WRAMC	Walter Reed Army Medical Center	390	44.3
OVERALL	CPDR National Database	879	100.0

Table II. Overall characteristics of 879 radical prostatectomy patients prior to treatment

Variable	Patients (n)	%
Pretreatment total testosterone (ng/dL)		
<200	110	12.5
200-299	203	23.1
300-399	262	29.8
400-499	174	19.8
>500	130	14.8
Mean/Median	362.4/348.0	
Race		
Not Black	655	74.6
Black	207	23.5
Unknown	17	1.9
Age (yr)		
<55	129	14.7
55-59	162	18.4
60-64	259	29.5
65-70	241	27.4
>70	88	10.0
Mean/median	62.3/63.3	
Pretreatment/diagnosis PSA (ng/mL)		
0-4	157	17.9
4.1-10	532	60.5
10.1-20	114	13.0
>20.1	32	3.6
Unknown	44	
	5.0	
Mean/median	7.4/5.7	
Pretreatment alkaline phosphatase (U/L)		
<75	411	46.8
75-99	295	33.6
>100	99	11.3
Unknown	74	8.4
Mean/median	77.6/75.0	
Pretreatment prostatic acid phosphatase (ng/mL)		
<1.00	185	21.1
1.00-1.99	355	40.4
2.00-2.99	104	11.8
>3.00	76	8.6
Unknown	159	18.1
Mean/median	1.7/1.4	
Biopsy Gleason (WHO) score		
<= 4	90	10.2
5-6	497	56.5
7	162	18.4
8-10	39	4.4
Unknown	91	10.3
Pretreatment serum creatinine (mg/dL)		
<=1.0	455	51.8
1.1-1.3	343	39.0
>1.3	63	7.2
Unknown	18	2.0
Mean/median	1.1/1.0	
Clinical stage		
<=cT1	485	55.2
cT2a	229	26.1
cT2b	97	11.0
cT2c	54	6.1
cT3-T4	4	0.5
Unknown	10	1.1
Treatment of BPH		
Yes	183	20.8
No	696	79.2

Abbreviations: PSA = prostatic-specific antigen; WHO = World Health Organization; BPH = benign prostatic hypertrophy

Table III. Surgical factors in 879 radical prostatectomy patients

Variable	Patients (n)	%
Treatment modality		
Primary RP only	827	94.1
RP + Adjuvant*	52	5.9
Pathologic Gleason (WHO) score		
<=4	16	1.8
5-6	438	49.8
7	320	36.4
8-10	78	8.9
Unknown	27	3.1
Pathologic stage		
<=pT2	514	58.5
pT3a	219	24.9
pT3b	56	6.4
pT3c	54	6.1
pT4	8	0.9
Unknown	28	3.2
Nerve sparing		
Unilateral	136	15.5
Bilateral	278	31.6
Not done	465	52.9
Margin status		
Pos	275	31.3
Neg	604	68.7
Capsule status		
Pos	279	31.7
Neg	600	68.3
Seminal vesicle status		
Pos	64	7.3
Neg	815	92.7
Node status		
Pos	15	1.7
Neg	864	98.3

**Adjuvant treatments consist of androgen ablation or external beam radiation*
Abbreviations: RP = radical prostatectomy; WHO = World Health Organization

Table IV. Relationship of pretreatment testosterone to patient demographics and surgical pathology- a non-parametric univariate analysis

	Testosterone (ng/dL)			
Variable	**Mean**	**Median**	**Range**	**p Value**
Pathologic stage				0.041*
pT1-T2	373.2	356.4	19-1490	
pT3-T4	348.9	340.0	30-846	
Race				0.363
Not Black	361.0	343.0	30-1490	
Black	369.6	362.8	33-846	
Age (yr)				0.103
<55	383.3	370.0	92-846	
55-59	347.9	330.0	19-704	
60-64	375.5	360.0	91-917	
65-70	350.2	348.0	30-901	
>70	353.4	323.0	40-1490	
Pretreatment/diagnosis PSA (ng/mL)				0.269
0-4	365.4	350.0	103-1490	
4.1-10	364.4	356.2	19-901	
10.1-20	351.6	339	34-700	
>20	329.6	301.5	100-810	
Pretreatment alkaline phosphatase (U/L)				0.523
<75	355.2	342.0	19-901	
75-99	369.0	348.0	34-1490	
>100	358.8	348.0	110-917	
Pretreatment prostatic acid phosphatase (ng/mL)				0.044*
<1.00	355.1	340.0	19-917	
1.00-1.99	353.5	339.0	40-1490	
2.00-2.99	341.9	343.5	30-880	
>3.00	395.4	390.0	110-846	
Biopsy Gleason (WHO) score				0.834
<= 4	359.1	354.5	30-880	
5-6	367.3	352.0	19-1490	
7	360.1	336.3	34-901	
8-10	343.7	349.7	110-665	
Pretreatment serum creatinine (mg/dL)				0.860
<=1.0	362.6	346.0	19-917	
1.1-1.3	359.1	350.0	40-1490	
>1.3	356.5	320.0	33-901	
Clinical stage				0.784
cT1	357.2	342.0	33-917	
cT2	370.1	355.5	19-1490	
cT3-T4	344.2	365.0	157-490	
Pathologic Gleason (WHO) score				0.381
<=4	311.1	307.5	170-470	
5-6	367.0	350.5	33-1490	
7	365.1	344.5	91-901	
8-10	343.2	348.9	30-665	

*** Significant values**

Abbreviations: PSA = prostatic-specific antigen; WHO = World Health Organization

Table V: Significant independent predictors of extraprostatic disease (pT1-T2 versus pT3-T4) – a multivariate logistic regression analysis*

Variable	Odds Ratio	95% CI	p Value
LogPSA	1.814	1.347-2.443	<0.0001
Biopsy Gleason (WHO) score			0.0160
2-4 vs 5-6	1.765	1.023-3.047	
2-4 vs 7	2.624	1.402-4.912	
2-4 vs 8-10	2.782	1.100-7.034	
Prostatic acid phosphatase (ng/mL)	1.196	1.019-1.404	0.0287
Total testosterone	0.999	0.998-1.000	0.0464

*Only *significant predictors shown*
Abbreviations: PSA = prostatic-specific antigen; WHO = World Health Organization

Table VI. Selected factors and their correlation with biochemical recurrence--univariate analysis

Factor	No. of patients	3-year Biochemical Recurrence Rate	5-year Biochemical Recurrence Rate	p Value
Race				0.0002
Not Black	571	15%	25%	
Black	176	30%	39%	
PSA (ng/mL)				<0.0001
0-4	137	9%	25%	
4.1-10	463	16%	23%	
10.1-20	103	28%	45%	
>20	25	50%	55%	
PAP (ng/mL)				0.0027
<1.00	161	13%	22%	
1.00-1.99	305	19%	27%	
2.00-2.99	92	17%	37%	
>3.00	66	30%	41%	
Pathologic Gleason (WHO) score				<0.0001
<=4	15	22%	22%	
5-6	378	9%	17%	
7	271	23%	36%	
8-10	71	45%	58%	
Pathologic stage				<0.0001
pT1-T2	415	10%	16%	
pT3-T4	343	28%	42%	
Testosterone (ng/dL)				0.467
<200	97	24%	32%	
200-299	179	17%	33%	
300-399	220	21%	26%	
400-499	149	15%	35%	
>500	113	13%	16%	
Testosterone (ng/dL)				0.347
<=300	276	20%	32%	
>300	482	17%	26%	

Abbreviations: PSA = prostatic-specific antigen; PAP = prostatic acid phosphatase; WHO = World Health Organization

Figure I. Low pretreatment total testosterone levels predict extraprostatic disease in radical prostatectomy patients

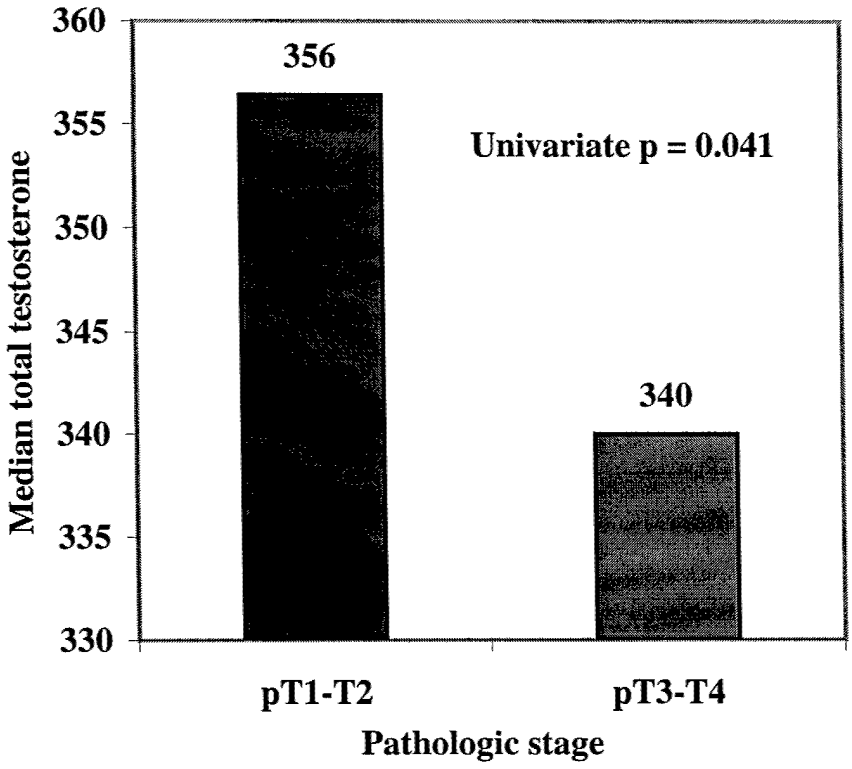
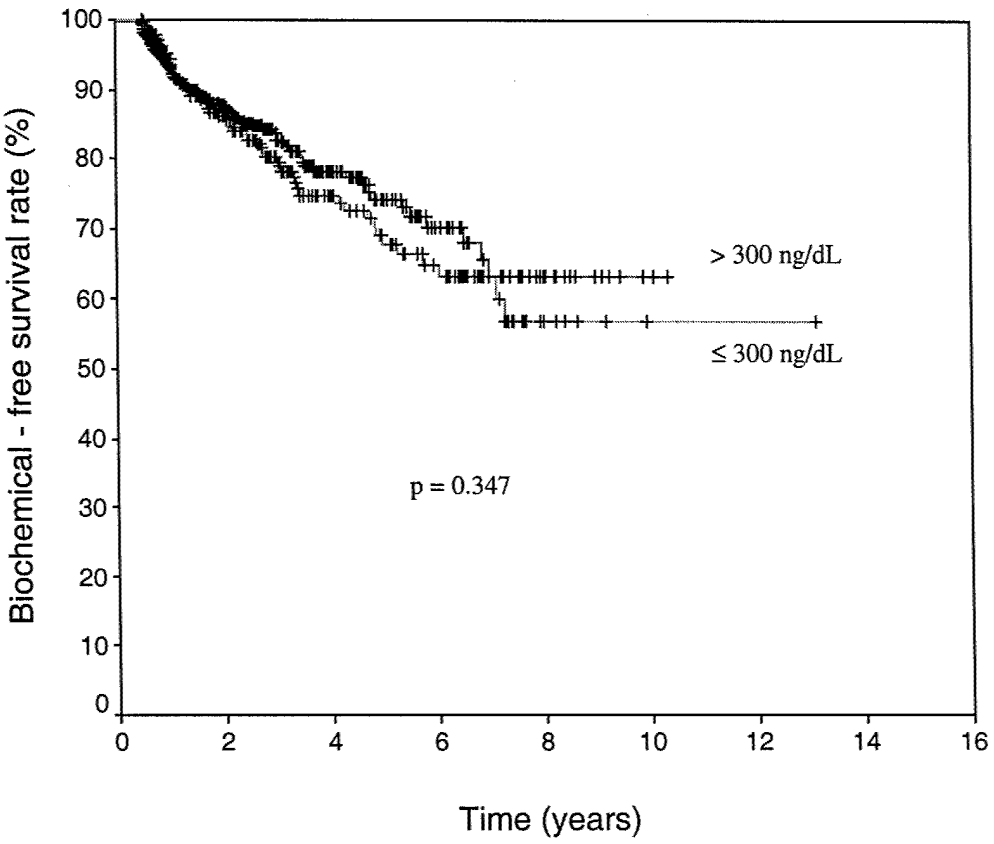


Figure II. Low pretreatment total testosterone does not significantly predict PSA recurrence after radical prostatectomy (Mean follow-up 37.7 months)



Appendix 5 Accepted as moderated poster in AUA 2003).

An algorithm with preoperative variables to predict PSA recurrence in prostate cancer patients receiving radical prostatectomy

Julian Wu, Leon Sun, Judd W. Moul, Holly Wu, David G. McLeod, Christopher Amling, Raymond Lance, John Foley, Wade Sexton, Leo Kusuda, Andrew Chung, Douglas Soderdahl, Timothy Donahue, Lionel Banez.

Center for Prostate Disease Research (CPDR), Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD 20814

Objectives: To characterize the relationship between PSA recurrence and preoperative factors and construct a equation of relative risk of recurrence to predict PSA recurrence in patients post radical prostatectomy.

Methods: 1450 patients receiving radical prostatectomy (RP) from 1988 to 2001 were retrieved from the CPDR National Database. Patients who received neoadjuvant and adjuvant treatment were excluded. The median follow-up was 3.1 years (0.5-12.4). All the patients had complete information of diagnosis age, race, clinical stage, diagnosis PSA, biopsy Gleason sum, total number of biopsy cores and number of cancer positive cores. PSA recurrence was defined as post-treatment PSA > 0.2 ng/ml. Effect of different ratio of cancer-positive biopsy cores over total biopsy cores (<34%, 34 – 66%, >66%) on PSA recurrence was assessed with Kaplan-Meier method. The multivariate Cox regression was used to identify preoperative variables predicting PSA recurrence.

Results: In 1450 patients, 427 (29.4%) had PSA recurrence. The 3-year and 8-year PSA recurrence-free survivals were 70.9% and 52.9% respectively. Univariate Log-rank test showed that the higher ratio of cancer-positive cores over total biopsy cores was, the worse PSA recurrence-free survival (p=0.033). In multivariate Cox model, race, diagnostic PSA and biopsy Gleason score were the three most significant predictors of PSA recurrence, and the ratio of cancer-positive biopsy cores over total biopsy cores was not an independent factor for predicting PSA recurrence. The relative risk of recurrence was calculated as $\exp(0.261 * \text{race}_{\text{black}} + 0.067\text{PSA}_{\text{ST}} + 0.130 * \text{biopsy Gleason sum})$, where PSA_{ST} indicates a sigmoidal transformation of PSA.

Conclusions: Race, diagnostic PSA and biopsy Gleason sum, rather than the ratio of positive biopsy cores over total biopsy cores, were prognostic variables for prediction of PSA recurrence in patients undergoing radical prostatectomy.

Key word: Prostate cancer, PSA recurrence, radical prostatectomy, Biopsy
Topic: Advanced

Abstract #: 105529
Abstract Title: AN ALGORITHM WITH PREOPERATIVE VARIABLES TO PREDICT PSA RECURRENCE IN PROSTATE CANCER PATIENTS RECEIVING RADICAL PROSTATECTOMY

Dear Dr. Sun:

I am happy to inform you that the Program Abstract Review Committee has accepted your abstract for presentation in a moderated poster session at the 2003 Annual Meeting of the American Urological Association to be held in, Chicago, Illinois, April 26-May 1, 2003. Complete details regarding your presentation are listed below:

Session Title: Prostate Cancer: Advanced (II)
Session Date: Tuesday, April 29, 2003
Session Time: 3:30 PM - 5:30 PM
Abstract Publication #: 1490
Location/Room#: E450

You may begin to set up your poster one half hour before your session begins and it must remain for the entire duration of the session. Instructions For Poster Presentations, which you are required to READ VERY CAREFULLY, will be available on the AUA Accepted Abstract Lookup Site at http://aua03.agora.com/grader/lookup.asp beginning December 27, 2002, If you have any questions regarding your presentation, please contact Cyndy Sprague, AUA Meeting Planner at 800-282-7077, x3031 (within the U.S.) or 713-622-2700 x3031 (outside the U.S.).

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Thank you and we look forward to seeing you in Chicago.

Sincerely,

Carl A. Olsson, M.D.
AUA Secretary and Program Committee Chair

Appendix 6 Accepted as moderated poster in AUA 2003).

Natural history of prostate cancer in 3605 CPDR patients receiving radical prostatectomy and factors affecting post-treatment clinical metastasis in PSA era.

Leon Sun, Judd W. Moul, Julian Wu, David G. McLeod, Christopher Amling, Raymond Lance, John Foley, Wade Sexton, Leo Kusuda, Andrew Chung, Douglas Soderdahl, Timothy Donahue, Michelle Zhao, Jack Chang.

Center for Prostate Disease Research (CPDR), Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD 20814

PURPOSE: This study was to characterize the natural history of prostate cancer in patients receiving radical prostatectomy (RP) and the associations between clinical metastasis and prognostic variables.

METHODS: A total of 3605 patients receiving radical prostatectomy between 1988 and 2001 were retrieved from the CPDR National Database. Patients who received neoadjuvant and adjuvant treatment were excluded. PSA recurrence was defined as post-treatment PSA > 0.2 ng/ml. Minimal follow-up was > 0.5 years. Post-treatment PSA doubling time was calculated. The association among clinical metastasis, pathological stages, Gleason sum and interval between PR and PSA recurrence were characterized with nonparametric test, Kaplan-Meier survival analysis and Cox regression analysis.

RESULTS: Among 3605 RP patients, the percentage of diagnostic PSA groups of > 4, 4 - 10, 10.1 - 20, and > 20 ng/ml were 20.5, 57.8, 15.9, and 5.8, respectively. 8.2% of patients had pathological Gleason sum > 7. Pathological stages of T1, T2 and T3 were 1.2%, 57.8% and 41.0%, respectively. The rate of PSA recurrence was 32.3% (1165). Of PSA recurrence cases, 7.6% (88) developed clinical metastatic disease. PSA recurrence-free and clinical metastasis-free survival were 85 vs 97.6% at year 1, 64.8 vs 91.0% at year 5, and 56.2 vs 86.1% at year 8. Kaplan-Meier analysis showed that PSA doubling time <10 months and pathological Gleason sum > 7 were significantly associated with clinical metastasis ($p < 0.01$). Multivariate Cox regression model showed that hazard ratio of pathological Gleason sum, PSA doubling time (< 10 months), and interval between RP and PSA recurrence (< 1 year) was 0.468 ($p = 0.03$), 2.235 ($p = 0.02$), and 2.026 ($p = 0.03$), respectively.

CONCLUSIONS: In PSA era (since 1988), the natural history of prostate cancer after radical prostatectomy has been changed with significantly improved clinical metastasis-free survival (83.5% at year 10). Variables of PSA doubling time < 10 months, Gleason sum, and PSA recurrence time < 1 year affect clinical metastasis.

Key word: Prostate cancer, metastasis, Recurrence, PSA, Radical prostatectomy, natural history

Topic: Advanced

Leon Sun
Center for Prostate Disease Research
1530 East Jefferson Street
Rockville, MD 20852
USA

Abstract #: 102841
Abstract Title: NATURAL HISTORY OF PROSTATE CANCER IN 3605 CPDR PATIENTS RECEIVING RADICAL PROSTATECTOMY AND FACTORS AFFECTING POST-TREATMENT
CLINICAL METASTASIS IN PSA ERA

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Session Date: Tuesday, April 29, 2003
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